<u>Ch. 1 Intro and Review</u> <u>1.1 Intro to Organic Chemistry</u> "Organic":

"Organic Chemistry":

- Focus on carbon, with H, N, O, and halogens all major contributors
- Biochemicals are all carbon-based
 - Food, hair, skin, muscles, etc.
 - Clothes, plastics, fuels, etc.

The abundance of carbon, by mass:

Universe	<<0.1%	
Earth	<1%	
Body	18% (60% of body mass is water)	
Non-water body mass	45%	

>90% of known molecules are organic!

Why is carbon so special?

1. Versatile bonding! 4 covalent bonds per carbon enables:

a.

b.

- 2. Modest Electronegativity enables:
 - a. strong bonds to other C's, H's, and other nonmetals

Orbitals and Bonding: Review (Chapter 1:2-5)

- 1. Atomic orbitals for 2nd-row elements (C, N, O):
- Note: for organic, we won't need to fuss with d or f orbitals
- 2. Valence electrons: electrons in an atom's outside shell
- **3.** Octet Rule: atoms transfer or share electrons to obtain a filled shell (which is 8 for C, N, O, halogen)
 - Note: <u>never</u> draw C, N, or O with > 8 electrons!!!
- 4. Bond Types:

a.	Covalent bonds	H ₂
•	Between <u>nonmetals</u>	
•	Involve shared electrons	H ₂ O
b.	<u>Ionic</u> :	
•	Negligible sharing of electrons	
•	Metals transfer electron(s) to nonmetal	LiF
•	If formula has a <u>metal</u> , assume <u>ionic</u>	
	bonding	
•	Special case of ionic bonding in	
	absence of metals: ammonium salts	NH4Cl

Normal Bonding (Chapter 1)

	Valence	Valence	Lone
	Electrons	Bonds	Pairs
	4	4	0
N	5	3	1
-0 :	6	2	2
Н—	1	1	0
:CI— :Br—	7	1	3

Summary of Normal, Ideal Bonding (No Formal Charge)

Rules for Drawing Lewis structures for organic molecules: (Ch 1:4,5)

- 1. Try to provide normal bonding for C, N, O atoms <u>if possible</u>. (Works > 95% of time)
- 2. Double or triple bonds will often be involved.
 - Double or triple bonds are often required to achieve normal bonding.
- 3. In any formula that has a charge, there will always be an atom with that formal charge.
- 4. In any formula that includes a metal, assume ionic bonding.
 - Assume positive charge for the metal,
 - Assume negative charge for the organic portion.
- 5. Do not draw bonds between nonmetals and metals, as if they were covalently bound.
- 6. Be sure to specify the formal charge on any atom that has formal charge.
- 7. Always be aware of how many lone pairs are on any atom
 - Note: We will often omit lone pairs. But you must know when they are there!

Lewis Structure Practice

- 1. Draw Lewis structures for the following formulas: (Include lone pairs or formal charges if necessary)
 - a. CH₃CH₃ b. CH₃CH₂OH

c. CO ₂	d.	HCN
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e. CH₃CHO

f. NaOCH₃

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Formal Charge (Section 1.7): When an atom does not have its normal bonding

- Atoms with formal charge dominate reactivity. Therefore the ability to recognize and identify atoms with formal charge is really important!
- <u>Skills</u>:
 - 1. Identify the formal charge for any atom that does not have normal bonding
 - 2. Identify the number of bonds and lone pairs associated with any atom whose formal charge is specified
- Note: <u>Designation of formal charge is required</u>. If you don't write the charge sign next to an atom that should have formal charge, you will lose test points!

Formal Charge Equations:

- 1. FC = group # (bonds + unshared e's) (use to calculate FC)
- 2. Group # FC = bonds + unshared electrons (given formal charge, use to find lone pairs)

Practical:	(memorize)
С	4 bonds \leftarrow neutral
	3 bonds and zero lone pairs $\leftarrow \rightarrow$ cation +1
	3 bonds and one lone pair \rightarrow anion -1
Ν	4 bonds \leftarrow cation +1
	3 bonds and one lone pair \rightarrow neutral
0	3 bonds and one lone pair \leftarrow cation +1
	2 bonds and 2 lone pairs \longrightarrow neutral
	1 bond and three lone pairs \rightarrow anion -1

FORMAL CHARGE

# of Bonds	С	Ν	0	F
4	0	+1		
3	-1 or	0	+1	
	+1			
2		-1	0	
1			-1	0

Chem 350 Jasperse Ch. 1 Notes

Formal Charge Practice (Section 1.7)

1. Assign any *formal charges* to atoms that need them:

 $\begin{array}{cccccccc} H & H & H & H & H & H \\ H - C - C - C - H & H - C - C - C - H & H & C \\ H & H & H & H & H \end{array}$





2. Fill in lone pairs on any atoms that need them (whether atoms with formal charge or neutral atoms):



Notice: With the exception of carbocations, all other C/N/O atoms end up with a combined total of four when you sum up their bonds and lone-pairs. So apart from carbocations, if you know the number of bonds, you can fill in the correct number of lone pairs without even thinking much!

Electronegtivity and Bond Polarity (Section 1.6)

Electronegativity: the ability to "hog" electrons in covalent bonds -when two atoms are unequal, one will always attract bond electrons more strongly than the other

-the more electronegative atom has a δ - charge, the less electronegative atom a δ + charge

Н 2.2						Patterns: 1. Increases left to right
		C 2.5	N 3.0	0 3.4	F 4.0	 Increases bottom to top C-H bond are pretty comparable, essentially nonpolar
					Cl 3.2	 C-other non-metal, C is always less electronegative, δ+ on C C-metal, C is always more
					Br 3.0	electronegative, δ- on C
					I 2.7	

<u>1.8 Ionic Structures</u>

1. If you see a metal in a formula, treat it as ionic rather than covalent/molecular

- a. -always put a positive charge on the metal
- b. -never draw a "bond" between the metal and the non-metal
- **c.** -always figure there must be a negative charge on the non-metal portion of the formula, with a formal negative charge on something
- 2. The one time you see ions without metals is with ammonium ions

LiOH

NaH

NH₄OCH₃

Structural Formulas (Section 1-10)

- 1. Full Structural Formulas
- 2. Condensed Formulas
- 3. Line-Angle (Skeletal) Formulas

Since organic structures are large and complex, full Lewis structures are often a hassle. You'll need to be proficient in both condensed and line-angle formulas.



<u>Condensed Formulas:</u> Central atoms are shown with attached atoms, essentially in <u>sequence</u>

- Challenges:
 - 1. Handling parentheses
 - 2. Handling double and triple bonds
 - 3. Handling branches
 - 4. Handling ketones/aldehydes/esters/amides/carboxylic acids
 - 5. In general, recognizing when an oxygen is double-bonded off a carbon, and when it is single bonded both to carbon and to something else.

Line-Angle (Skeletal) Formulas:

- 1. Each vertex represents a carbon
- 2. C-H bonds are often omitted: assume enough H's to give four bonds or the appropriate formal charge
- 3. Oxygen and Nitrogen atoms must be specified, and O-H and N-H bonds are not omitted
- Line-angle formulas are routinely the fastest and cleanest to draw.
- Line-angle is essential and optimal for showing 3-dimensional organic shape.

Formula Practice (Section 1-10)

3. Time race: Draw as many copies of C_6H_{14} hexane as you can in 20 seconds:

Full:

Condensed:

Line-Angle:

Draw the full structure, given the condensed structure.

Point being illustrated

- a. CH₃CH₂OH
- b. (CH₃)₂CHCH₂NH₂
- $c. \quad CH_2 CHCl$
- d. CH₃CHO
- $e. \quad CH_3CO_2H$

Fill in the full structure, including attached hydrogens and attached lone pairs, for the following line-angle structures. If given a condensed structure, convert it to a line-angle.



j. CH₃CH₂CH₂CH₂CH₃

k. CH₃CO₂H

Resonance Structures (Section 1:9)

• Online students, watch: <u>https://www.youtube.com/watch?v=DTow76zAZ98</u> Sometimes a single Lewis structure does not provide an adequate picture.

Example: O₃ (ozone)

O₃



-1.2 0 -1.2 C Actual Species Is a

Hybrid of the Resonance Forms

Notes/observations:

- 1. Neither form A nor B can avoid formal charges.
 - The majority of resonance situations have some formal charge involvement
- 2. The <u>real molecule</u> is <u>hybrid</u>: see picture C
 - The central oxygen has + charge
 - Each of the outside oxygens is -1/2
 - Both of the bonds to the outside oxygens are equal in length/strength
 - The actual length/strength of the oxygen-oxygen bonds reflect 1.5 bonds (shorter and stronger than single bonds; longer and weaker than double bonds)
- 3. Why not just draw the hybrid?
 - Hard to do, without first working through resonance structures first.
 - Hard to keep track of the electrons, which help explain reactivity/mechanism
- 4. <u>Resonance Recognition</u>: When are Two Structures related as Resonance Structures?
 - Atoms must be connected in exactly the same way.
 - Resonance forms differ only in the placement of electrons.
 - If two Lewis structures have the same atomic connectivity, but differ <u>only</u> in the placement of some electrons/formal charges, they are related as resonance structures.
 - If the placement/connectivity of atoms differ, then the two structures are <u>not</u> resonance structures (they may perhaps be related as "isomers", see later.)
 - KEY: FOR RESONANCE STRUCTURES, ELECTRONS MOVE BUT ATOMS DO NOT MOVE. IF ATOMS MOVE, YOU DON'T HAVE RESONANCE STRUCTURES
 - Note: The real molecule is represented by the hybrid, and electrons are not actually jumping back and forth.
- 5. Resonance involves the **delocalization** of electrons and charge
 - In ozone, neither outside oxygen gets stuck with a full negative charge. The charge is shared so that both outside oxygens have a more manageable -1/2 charge
 - This delocalization of electrons/charge is stabilizing.
 - KEY: RESONANCE IS STABILIZING
- 6. Resonance always involves electrons in double bonds and/or lone pairs (π electrons)
- 7. "Allylic resonance": The most frequent resonance situation is when a charged atom is attached to a double bonded atom
- 8. When resonance structures are equal in stability, the hybrid is the average of the forms
- 9. When resonance structures are unequal, the more stable structure dominates the hybrid
 - <u>Ranking Stability:</u>
 - More bonds \rightarrow more stable (but don't exceed octet rule!). (<u>Priority rule</u>)
 - Bonds being equal, consider <u>electronegativity</u> (tiebreaker rule):
 - <u>negative charge</u> is better on <u>more electronegative atom;</u>
 - **positive charge** is better on **less electronegative atom**

Resonance Problems

1. Which of the following are related as resonance structures?



2. Which Resonance Structure is Better and would make a more than 50% contribution to the actual hybrid? Why, bonds or electronegativity?



3. Draw a resonance structure for the following



Some Arrow-Pushing Guidelines (Section 2.14)

- 1. Arrows follow <u>electron movement</u>.
- 2. Some rules for the appearance of arrows
 - The arrow must begin from the electron source. There are two sources:
 - a. An atom (which must have a lone pair to give)
 - b. A bond pair (an old bond that breaks)
 - An arrow must always point directly to an <u>atom</u>, because when electrons move, they always go to some new atom.
- 3. Ignore any Spectator Atoms. Any metal atom is always a "spectator"
 - When you have a metal spectator atom, realize that the non-metal next to it must have negative charge
- 4. Draw all H's on any Atom Whose Bonding Changes
- 5. Draw all lone-pairs on any Atom whose bonding changes
- 6. <u>**KEY ON BOND CHANGES**</u>. Any two-electron bond that changes (either made or broken) must have an arrow to illustrate:
 - where it came from (new bond made) or
 - an arrow showing where it goes to (old bond broken)

7. <u>Watch for Formal Charges and Changes in Formal Charge</u>

- If an atom's charge <u>gets more positive</u> ⇒ it's donating/losing an electron pair ⇒ <u>arrow must emanate from that atom or one of it's associated bonds.</u> There are two "more positive" transactions:
 - <u>When an anion becomes neutral</u>. In this case, an arrow will emanate from the atom. The atom has donated a lone pair which becomes a bond pair.
 - <u>When a neutral atom becomes cationic</u>. In this case, the atom will be losing a bond pair, so the arrow should emanate from the bond rather than from the atom.
- If an atom's charge <u>gets more negative</u> ⇒ it's accepting an electron pair ⇒ <u>an arrow must point to that atom</u>. Ordinarily the arrow will have started from a bond and will point to the atom.

8. <u>When bonds change, but Formal Charge Doesn't Change, A</u> <u>"Substitution" is Involved</u>

- Often an atom gives up an old bond and replaces it with a new bond. This is "substitution".
- In this case, there will be an incoming arrow pointing directly at the atom (to illustrate formation of the new bond), and an outgoing arrow emanating from the old bond that breaks

Examples of "Arrow Pushing" and "Mechanism" (Section 2-14)

Reaction: $HO^{\bigcirc} + CH_3Br \longrightarrow HOCH_3 + Br^{\bigcirc}$

Mechanism, with arrows to show how electrons move, how the new bond forms, and how an old bond breaks:

$$HO: + H-C - Br: \longrightarrow HO - C-H + Br: \bigcirc$$

Notes:

- Arrows are drawn to show how electron pairs are moving as new bonds form or old bonds break.
- Mechanisms help us to understand and generalize when and why bonds make or break, so that we can understand when and why reactions will occur and what products will form.
- Each arrow always goes from an electron source (either an atom with a lone pair or else a bond pair) to an acceptor atom
- <u>Terms:</u>
 - a. "<u>Nucleophile</u>" = source of electon pair ("Lewis base")
 - b. "<u>Electrophile</u>" = acceptor
- ("Lewis acid")
- c. An arrow always proceeds from a nucleophile and points toward an electrophile.
- d. Arrow-pushing is very helpful in relating two resonance structures
- 1. Use arrows to show how the electrons "move" from the first to the second resonance structures:



2. Use arrows to show the mechanism for the following acid-base reaction.



3. Use arrows to show the mechanism for the following two-step reaction. For the first step, identify the "nucleophile" and the "electrophile".



Acid-Base Chemistry (Section 2:4-12)

Acidity/Basicity Table

Entry	<u>Class</u>	<u>Structure</u>	<u>Ka</u>	<u>Acid</u> <u>Strength</u>	Base	<u>Base</u> <u>Strength</u>
1	Strong Acids	H-Cl, H ₂ SO ₄	10 ²		0 ⊖ CI [⊖] , HO-S-O 0	
2	Hydronium	H ₃ O ⁺ , ROH ⁺ cationic	100		H ₂ O, HOR neutral	
3	Carboxylic Acid	R OH	10-5		R [↓] O⊖	
4	Ammonium Ion (Charged)	R, H R ^N R Charged, but only weakly acidic!	10 ⁻¹²		$ \begin{array}{c} R \\ N \\ R^{-} \\ N \\ Neutral, but basic! \end{array} $	
5	Water	НОН	10-16		_{но} Ө	
6	Alcohol	ROH	10-17		_{RO} Θ	
7	Ketones and Aldehydes	O a H	10-20		o	
8	Amine (N-H)	(iPr) ₂ N-H	10-33		(iPr) ₂ N [⊖] Li [⊕]	
9	Alkane (C-H)	RCH ₃	10-50			

Quick Checklist of Acid/Base Factors

- 1. Charge
- 2. Electronegativity
- 3. Resonance/Conjugation
- 4. Hybridization
- 5. Impact of Electron Donors/Withdrawers
- 6. Amines/Ammoniums
- When a neutral acids are involved, it's best to draw the conjugate anionic bases, and then think from the anion stability side.

More Detailed Discussion of Acid/Base Patterns/Factors to remember

- 1. Charge: all else equal, cations are more acidic than neutrals, and anions more basic than neutrals.
- 2. Electronegativity:
 - Acidity: H-X (halogen) > H-O > H-N > H-C
 - Basicity: $X \stackrel{\Theta}{\sim} < O \stackrel{\Theta}{\sim} < N \stackrel{\Theta}{\sim} < C \stackrel{\Theta}{\sim}$
 - Anion Stability: X > O > N > C =
 - Why: <u>The more stable the anion Z⁻ that forms, the more acidic the parent</u> <u>H-Z will be</u>. All acids H-Z must give up H⁺. The better off the resulting anion Z⁻ is, the more willing H-Z will be to sacrifice H⁺.
 - <u>The anion stability directly correlates the love for electrons.</u>
 - Notice three things:
 - ANION STABILITY and the ACIDITY OF A NEUTRAL ACID PRECURSOR ARE DIRECTLY RELATED.
 - ANION STABILITY and the BASICITY OF THE ANION ARE INVERSELY RELATED (more stable anion, less basic anion)
 - ANION BASICITY AND THE ACIDITY OF THE CONJUGATE ACID ARE INVERSELY RELATED (the stronger the acidity of the parent acid, the weaker the basicity of the conjugate anion)
 - KEY: WHEN THINKING ABOUT ACIDITY AND BASICITY, FOCUS ON THE ANION. THE STABILITY OF THE ANION DETERMINES ACID/BASE BEHAVIOR.
- 3. Resonance/Conjugation: Since anion resonance is stabilizing, <u>an acid that gives a</u> <u>resonance-stabilized anion is more acidic.</u> And an anion that forms with resonance will be more stable and less basic.
 - Oxygen Series Examples: Acidity: sulfuric acid > carboxylic acid > water or alcohol
 Q Q

- Note: Resonance is often useful as a tiebreaker (for example, molecules in which both have O-H bonds and both have equal charge, so that neither the charge factor nor the electronegativity factor could predict acidity/basicity)
- NOTE: Resonance can sometimes (not always) trump electronegativity or even charge.
 - Example of resonance versus charge: A carboxylate anion, with serious resonance stabilization, ends up being so stabilized that it is even less basic than a neutral, uncharged amine! A hydrogen sulfate anion from sulfuric acid is less basic than not only neutral amines but also neutral oxygen (water, etc.)
- 4. Hybridization: For lone-pair basicity, (all else being equal), $sp^3 > sp^2 > sp > p$
- 5. Electron donating/electron withdrawing substituents:

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- Electron withdrawing substituents stabilize anions, so they increase neutral acidity and decrease anion basicity
- Electron donating substituents will destabilize anions, so they decrease neutral acidity and increase anion basicity.

6. Ammonium Cations as Acids and Neutral Amines as Bases

- Neutral amines are more basic than any neutral oxygen (electronegativity factor), and more basic than some resonance-stabilized oxygen anions.
- Ammonium cations are more acidic than neutral nitrogen compounds or most neutral oxygen compounds, but less acidic than oxygens that give resonancestabilized anions. (In this case, resonance factor trumps the charge factor).

Acid/Base Problems

5.

NH₂

Choose the More Acidic for Each of the Following Pairs: Single Variable Problems NH_3 $\oplus NH_4$ 1. ÕH₂ OH 2. OH NH_2 `CH₃ 3. 4. Ю

Rank the Acidity from $1 \rightarrow 5$, 1 being most acidic. (Think Anion! And Draw 6. Anion!)

NH₂

			0	
			Î	
HF	H_2O	CH ₃ NH ₂	Н ОН	CH_4

7. For the anions drawn in problem 6, rank them from $1 \rightarrow 5$ in terms of **basicity**.

Choose the More **Basic** for Each of the Following Pairs (Single Variable)



<u>Predicting Acid/Base Equilibria: Any acid base equilibrium favors the side that has the more stable, less reactive base</u>

6. Draw arrow to show whether equilibrium favors products or reactants. (Why?)

a.
$$H_2O + \bigcirc NH_2$$
 $\bigcirc OH + NH_3$
b. $H_2O + H \bigcirc \bigcirc \bigcirc$ $\bigcirc OH + H \bigcirc OH$

Generic acid/base reaction, with anionic base and neutral acid: HA + B^{\bigcirc} \longrightarrow A^{\bigcirc} + BH

Stronger acid \rightarrow weaker conjugate base

Weaker acid \rightarrow stronger conjugate base

- Acid-base reactions always favor formation of the weaker acid and weaker base
- The weaker acid and weaker base are always on the same side
- The more stable anion is the weaker base

THEREFORE:

- The equilibrium will always favor the WEAKER, MORE STABLE ANION
- IF YOU CAN IDENTIFY WHICH ANION IS MORE STABLE, YOU CAN PREDICT THE DIRECTION THE REACTION WILL GO.
- This logic can be used to predict whether an anion can successfully deprotonate a neutral species.
- 7. Can $H_3C \ominus$ deprotonate H_2O ?

Structure and Properties of Organics; Functional Groups

3-D Structure, Hybridization, and Orbitals (1.12-17)

<u>"VSEPR" and Shape:</u> <u>Valence Shell Electron Pair Repulsion (1.15,17)</u>

Online students: watch the following videos: (In face-to-face lecture, I'll probably show some physical models, which will not get displayed in the lecture video. So several minutes in the lecture video will be kind of useless to you without seeing the models. The two videos linked below will give you something as good, or probably better, to view....)

- Online students, watch review of VSEPR logic: https://www.youtube.com/watch?v=keHS-CASZfc
- Online students, watch more video with a bunch of tetrahedral and trigonal atoms, with reference to bond angles and hybridization: https://mediaspace.minnstate.edu/media/350-T1-VSEPR-Modeling-with-Spartan/1_1andi8t5

Concept: electron groups repel, determine structure

4 electron groups: tetrahedral, 109° angle

- 3 electron groups: trigonal planar, 120° angle
- 2 electron groups: linear, 180° angle
- 2 Types of "Electron Groups"
- 1. "B" = bonds to other atoms.
 - Whether it's a single, double, or triple bond, it still counts as one "electron group" or one "bond group"
- 2. "L" = Lone pairs

	Electron	Bond		Remaining
B+L	Geometry	Angle	Hybridization	π -orbitals
4	Tetrahedral	≈109°	sp ³	0
3	Trigonal	≈120°	sp^2	1
	Planar			
2	Linear	≈180°	sp	2

EXAMPLES



Chem 350 Jasperse Ch. 2 Notes

Guidelines for Drawing Models:

A. In-Plane/Out-of-Plane

- Designate an atom in front of plane with a wedge
- Designate an atom **<u>behind</u>** plane with a <u>hash</u>
- Designate an atom in the plane plane with a straight line

B. 3-D Perspective

- 1. Keep as many atoms as possible in a single plane (plane of the paper) by zigzagging. Connections within the paper are drawn with straight lines.
- 2. Use wedges to indicate atoms that are in front of the plane.
- 3. Use hashes to indicate atoms behind the plane.

C. For any tetrahedral atom, only 2 attachments can be in the plane, 1 must be in front, and 1 behind. (Online students:

https://mediaspace.minnstate.edu/media/350-T1-VSEPR-Modeling-with-Spartan/1_1andi8t5

- a. -if the two in the plane are "down", the hash/wedge should be up
- b. -if the two in plane are "up", the hash/wedge should be down.
- c. -the hash/wedge should never point in same direction as the in-plane lines, or else the atom doesn't looks tetrahedral
- d. -for polyatomic molecules, it is strongly preferable to NOT have either of the inplane atoms pointing straight up. Straight-up in-plane atoms do not lend themselves to extended 3-D structures.



Good! Look tetrahedral

Bad! These don't look tetrahedral!







0

Η′



H



Draw: C₂H₆

 C_4H_{10}

CH₃COCH₃

CH₃CH=CHCl

Hybrid Orbitals; π bonding (1:12-15)

$1s + 3p \rightarrow 4 sp^3$ hybrids	109°
$1s + 2p (+1 \text{ unhybridized } p) \rightarrow 3 \text{ sp}^2 \text{ hybrids } (+1 \text{ unhybridized } p)$	120°
$1s + 1p(+2 \text{ unhybridized } p's) \rightarrow 2 \text{ sp hybrids} (+2 \text{ unhybridized } p's)$	180°

Why does hybridization occur?

- Hybrid orbitals are big and point in one direction. Their directionality leads to better overlap which leads to strong bonds.
- Hybrid orbitals leads to nice VSEPR angles

If hybridization is so great, why aren't pure monatomic atoms hybridized?

- For an isolated atom, having 1 s and 3 p atomic orbitals is better than 4 sp^3 hybrid orbitals
- However, when covalent bonds can result, the small price of hybridizing is paid off a • thousandfold by the payoff of making strong, good VSEPR bonds

If hybridization is so great, why aren't all carbons sp³ hybridized? Why do some stay sp² or sp, and withhold some p orbitals from hybridization?

- p orbitals are withheld from hybridization for the sole purpose of using them to make π bonds.
- Only when double bonds or triple bonds are involved is the hybridization less than the full sp³
- Each π bond requires the attached atoms to use p orbitals

2 Kinds of Covalent Bonds

π

- sigma (σ) bonds: electron density is along the axis between the nuclei $-\sigma$ bonds always involve the overlap of s or s-containing hybrids (s, sp, sp², sp³)
- pi (π) bonds: electron density is either above/below or before/behind, but not along the internuclear axis
 - π bonds involve the overlap of parallel p orbitals

The first bond in any bond (whether single, double, or triple), is a σ bond. The "extra" bonds in a double or triple bond are π bonds. Bond σ

Single 0 1 Double 1 1 Triple 1 2

 π bonds are weaker and more reactive than σ bonds. Most organic reactions involve π bonds

Bond Rotations, Structural Isomers, and Stereoisomers (1.18-19)

Rotation is allowed for single bonds

- No bonds break, the sigma bond is fine
- Rotation is forbidden for double bonds
- The π -bond overlap breaks, between the two p orbitals that need to be parallel

isomers-different compounds with the same molecular formula.

structural isomers (or constitutional isomers)-isomers that have their atoms connected in a different order.



stereoisomers (or configurational isomers)-isomers in which atoms are joined in the same order but differ in the way their atoms are arranged in space.

- Stereoisomers have the same condensed formula (if not, they aren't stereoisomers)
- Stereoisomers can not be interconverted by bond rotation or by being turned over
- If two things can be interconverted by bond rotation or being turned over, then they aren't stereoisomers!
- Stereoisomers are subdivided into two categories: enantiomers and diastereomers.
 Diastereomers: have cis/trans relationship



$$\begin{array}{cccc}
H & H & CH_3 \\
C=C & C=C \\
CH_3 & H_3C & H \\
cis & trans
\end{array}$$

• Enantiomers: have mirror image (left hand/right hand) relationship

Br

H Br Br H

Problem: For the following pairs of structures, classify whether they are related as <u>same</u>, <u>structural isomers</u>, or <u>stereoisomers</u>.

H₃C



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Polarity (2.1)

-molecular dipole: vector sum of bond and lone-pair dipoles

A simple molecule is totally nonpolar only if:

- 1. Central atom has no lone pairs
- 2. All attached atoms are the same

Practical:

- Lone pairs and O-H or N-H bonds usually dominate
- C-C, C-H, and C-halogen bonds are practically nonpolar or at best only weakly polar

Problems: Classify as totally nonpolar or polar.

a. CO ₂	b. CCl ₄	c. CH ₄	d. C ₄ H ₁₀
e. H ₂ O	f. NH ₃	g. CH ₃ CH ₂ OH	h. CHCl ₃

Intermolecular Forces and Boiling Points (2.2)

- 1. Hydrogen bonds (O-H or N-H)
- 2. Dipole-Dipole
 - Much weaker than hydrogen bonds
- 3. London Forces
 - Increases with increasing molecular weight

Intermolecular Forces impact:

- 1. Boiling points and melting points
- 2. Solubility

For Boiling Points:

- 1. If weight is about equal \rightarrow H-bonder > polar > nonpolar
- 2. If H-bonding/polarity is comparable: high mw > lower mw

Problem: Rank the boiling points, 1 being highest

<u>,</u>0, OH a. b.

 H_2 H₃C^{_}OH H₃C^COH c.

Polarity and Solubility (2.3)

2 Practical Rules:

- 1. The more N's or O's in a molecular, the greater it's water solubility
- 2. The more C's, the lower it's water solubility

Facts/Theory

- 1. "Like dissolves like"
 - enthalpy and entropy factors

Good solubility	Bad solubility
a. Polar solvent-polar solute	a. Polar solvent-nonpolar solute
b. Nonpolar solvent-nonpolar solute	b. Nonpolar solvent-polar solute

- 2. Water is very polar
- 3. Any molecules with N or O can H-bond with water (even if it can't necessarily H-bond itself) (Rule 1)
- 4. Adding C's adds C-C, C-H nonpolar bonds \rightarrow reduces water solubility (Rule 2)
- 5. Hydrocarbons and halocarbons are insoluble in water
 - Many other organics have low solubility in water
 - Depends on the ratio of nonpolar/polar, N or O to C

<u>Problems</u>: Circle the more water soluble of the following pairs:



<u>Problem</u>: Box the higher boiling in each pair. Does water solubility and boiling point always correspond? Why or why not?

Classification of Organic Compounds. The Functional Groups (2:16,17) Hydrocarbons: C + H only

0. Alkanes and Cycloalkanes

- a. Single bonds only
- b. Names end "ane" (methane, ethane, propane, etc.)
- c. "cycloalkanes": carbon rings
- d. alkanes are considered "nonfunctional"
 - no reactive π -bonds, lone pairs, heteroatoms, or highly polar bonds
- e. an "<u>alkyl group</u>" is <u>part</u> of a molecule that contains only C, H, and single bonds.
 - 1. Basically a part of the molecule that isn't going to be very reactive or "functional"
 - 2. Symbol: R

1. Alkenes C=C

- a. contain C=C double bond
- b. names end "ene" (ethane, propene, butene, etc.)

c. <u>double bonds can't rotate</u>

- a. rotation is allowed for single bonds, but is forbidden for double bonds
- b. Why:
 - 1. a single bond (σ) can rotate freely without compromising orbital overlap
 - 2. But a π -bond cannot rotate freely, because π -overlap breaks
 - The two π -bonded atoms have parallel and overlapping p orbitals. To rotate the bond completely breaks the π -bond half-way through the rotation.
 - The energy price is thus way too high.
- d. Restricted rotation results (sometimes) in cis/trans isomers

- e. A π -bond is much weaker than a σ -bond, and thus is far more reactive. Thus, an alkene is viewed as a "functional group" because it reacts ("functions")
- f. Functional groups and "R" groups:

2. Alkynes: Triple bonds Name end "yne"

3. Aromatics or Arenes: Resonance

Twelve To Remember: The Functional Groups



Chem 350 Jasperse Ch. 2 Notes

4. Haloalkanes

R-X

- bonds are polarized: R group is δ^+ , halogen is δ^-
- C-X bonds are often rather weak and breakable = "functional"

Oxygen Compounds

5. Alcohols

ROH

- a. contain OH group attached to an sp3 carbon
- b. names end "ol" (methanol, ethanol, etc.)
- c. Oxygen hybridization and shape:
 - sp3, tetrahedral electron geometry, approximately 109° bond angle
- d. Hydrogen-bonding: impacts boiling point and water solubility
- 6. Ethers ROR
 - a. Oxygen hybridization and shape:
 - sp3, tetrahedral electron geometry, approximately 109° bond angle
 - e. Don't hydrogen-bond themselves, so lower boiling than ROH of equal weight.
 - f. Oxygen lone pairs do hydrogen-bond to water hydrogens, so decent water solubility
 - g. Relatively low reactivity

7,8. Aldehydes, KetonesC=OAldehydesKetones

- a. C=O group = "carbonyl group"
- b. Carbonyl carbon: sp2, trigonal planar, 120° bond angles
- c. The carbonyl always has two other attachments, of which:
 - Formaldehyde has 2 H's attached to carbonyl
 - Aldehydes have one H attached to carbonyl
 - Ketones have no H's attached to carbonyl.
- d. Carbonyl bond is strongly polarized
 - Highly reactive
 - Highly electrophilic

9. Carboxylic Acids:

- Strong polarity and resonance stabilization of conjugate anions make these fairly acidic.
- Extremely important role in biological pH and biochemistry

10. Esters

- without OH bond, esters don't have the hydrogen bonding or acidity of carboxylic acids
- reactivity is similar to aldehydes and ketones, dominated by carbonyl

Nitrogen Compounds

11. Amines

- a. polar
- b. usually hydrogen bonders
- c. Nitrogen lone pairs are basic (primary chemical and biological role)
- d. Many drugs are amines
- 12. Amides

- a. polar
- b. proteins and enzymes consist of multiple amides
- c. nitrogen is flat, sp^2 , trigonal planar, thanks to resonance
- d. Nitrogen lone pair is not basic

The Functional Groups, R-Z

Functional Group Z	Name	Suffix (or Prefix) Used in Systematic Name	Nomeno Review	lature
-R	Alkane	-ane	methan-	1C 2C
$\rightarrow = \langle$	Alkene	-ene	propan- butan- pentan-	2C 3C 4C 5C
	Alkyne	-yne	heptan- octan- nonan-	0C 7C 8C 9C
	Arene	not responsible	decan-	10C
-X (Cl, Br, I, or F)	Haloalkane	halo-		
-OH	Alcohol	-ol		
-OR	Ether	not responsible		
Ц	Aldehyde	-al		
R	Ketone	-one		
ОН	Carboxylic Acid	-oic acid		
OR	Ester	-oate		
NH ₂	Amide	-amide		
-NH ₂	Amine	amino-		

# C's	Name	Formula	Bp (°C)	Structure
1	Methane	CH ₄	-162	H-(CH ₂)-H
2	Ethane	C_2H_6	-89	H-(CH ₂) ₂ -H
3	Propane	C_3H_8	-42	H-(CH ₂) ₃ -H
4	Butane	C4H10	0	H-(CH ₂) ₄ -H
5	Pentane	C5H12	36	H-(CH ₂)5-H
6	Hexane	C ₆ H ₁₄	69	H-(CH ₂) ₆ -H
7	Heptane	C7H16	98	H-(CH ₂) ₇ -H
8	Octane	C ₈ H ₁₈	126	H-(CH ₂) ₈ -H
9	Nonane	C9H20	151	H-(CH ₂)9-H
10	Decane	$C_{10}H_{22}$	174	H-(CH ₂) ₁₀ -H

ALKANE NAMES, Formulas, Properties (Memorize) (3.2,4)

Notes: (Including some alkane properties, Section 3.5)

- 1. Memorize names
- 2. Names all end in "ane"
- 3. From 5 up, come from Greek
- 4. Boiling points: more C's \rightarrow high boiling point (London force)
- 5. Formula: for <u>acyclic alkanes</u> \rightarrow C_NH_{2N+2}
 - Basically 2H per carbon (2N), plus 2 extra H's at the ends (+2)
 - Branched isomers for acyclic alkanes still have C_NH_{2N+2}
- 6. <u>Cyclic Alkanes</u>: names start in "cyclo" (cyclopentane, cyclooctane, etc.)
- 7. Formula for cyclic alkanes $\rightarrow C_{\rm N} H_{2\rm N}$
 - Basically 2H per carbon (2N), but without the extra two H's at the ends
 - Cyclic alkanes with side-chains still have C_NH_{2N}
- 8. Solubility: nonpolar
 - \rightarrow insoluble in water
 - \rightarrow soluble in nonpolar, hydrophobic solvents
- 9. Density: <1 (less than water)
 - \rightarrow float on top of water

Industrial Alkanes (3.5)

Name	# C's	Boiling Range	Use
Natural Gas	C1-C3	Gas	Fuel
	(70% methane)		
"Petroleum Gas"	C2-C4	<30°	Heating, Gas
Propane	C_3	-42°	Propane tanks,
			camping, etc.
Gasoline	C4-C9	30-180°	Car fuel
Kerosene	C8-C16	160-230°	Jet fuel
Diesel	C ₁₀ -C ₁₈	200-320°	Truck fuel
Heavy Oils	C ₁₆ -C ₃₀	300-450°	
Motor Oils		High temp	
Asphalt		Never Distills	
Coke		Never Distills	

Nomenclature of Alkanes (3.3-4)

Systematic IUPAC Rules for Branched and Substituted Alkanes

- 1. Longest continuous C-chain \rightarrow "core name"
- 2. Number core chain from an end nearest a substituent
- 3. Name substituents as "alkyl" groups:
- 4. Specify the location of substituents using numbers (hyphenate the #'s)
 - If >2 substituents, list alphabetically
 - Use di-, tri-, tetra- if the same substituent is repeated. (But ignore these in alphabetizing).

Punctuation Notes:

- Hyphenate numbers
- Do <u>not</u> put a space between substituents and the core name

Memorize	H ₃ C CH– H ₃ C	СН ₃ Н ₃ С-С- СН ₃		Include iso in alphabetizing
	isopropyi	t-butyl or tert-butyl		
Others	H ₂ H ₃ C C_C C H ₂ n-propyl (n for "normal")	$\begin{array}{c} H_2\\ H_3C \\ C \\ H_2 \\ H_2 \\ n-butyl \end{array}$	$\begin{array}{c} CH_3\\ H_3C \overset{CH}{\underset{H_2}{\overset{CH}{\overset{C}{\overset{H}}}} C \overset{C}{\underset{H_2}{\overset{H_2}{\overset{I}}{\overset{I}{\overset{I}{\overset{I}{\overset{I}{\overset{I}{\overset{I}{\overset{I}{\overset{I}{\overset{I}{\overset{I}{\overset{I}{\overset{I}}{\overset{I}{\overset{I}{\overset{I}{\overset{I}{\overset{I}{\overset{I}{\overset{I}{\overset{I}{\overset{I}}{\overset{I}{\overset{I}}{\overset{I}{\overset{I}{\overset{I}{\overset{I}}{\overset{I}{\overset{I}{\overset{I}{\overset{I}{\overset{I}{\overset{I}}}}}}}}}$	$\begin{matrix} \\ H_3C \\ C_{-}CH \\ H_2 \\ s-butyl \end{matrix}$

Special Names for Some 3 or 4-carbon Substituents

Another Classification System

Primary (1°): with one attached carbon Secondary (2°): with two attached carbons Tertiary (3°): with three attached carbons

$$c \stackrel{H}{\leftarrow}_{H^{10}} c \stackrel{C}{\leftarrow}_{H^{20}} c \stackrel{C}{\leftarrow}_{3^{\circ}}$$

Very Complex Substituents (Not responsible)

Substituent: (1-ethyl-2,3-dimethylpentyl) Overall: 9-(1-ethyl-2,3-dimethylpentyl)nonadecane

Nomenclature Example Problems



Structure, Conformations of Acyclic Alkanes (3.7)

A. "Conformations" = "Conformers" = "Rotamers" = different 3-D arrangements resulting from rotation around a single bond



B. "Newman Projections": look straight down one C-C bond

- Online students, watch: https://www.youtube.com/watch?v=1550xtF-u1k
- Online students, watch: https://www.youtube.com/watch?v=tEXtJLTmdDI
- 1. If both bonded carbons are tetrahedral, there will be three bonds extending from the front carbon, and three more bonds extending from the back carbon
- 2. Terms:
 - 1. <u>Dihedral angle</u>: angle between a bond on the front atom relative to a bond on the back atom
 - 2. Eclipsed: when bonds are aligned. 0°, 120°, 240°, 360° dihedral angles
 - 3. Staggered: when bonds are as far apart as possible: 60°, 180°, 300°
 - 4. <u>Skew</u>: anything else in between the eclipsed and staggered extremes



Energy: Staggered best, eclipsed worst

1. Why: <u>Torsional strain</u>. **Repulsion between bonding electron pairs** is reduced in the staggered conformation, and is worst in the eclipsed conformation.

<u>Rotation Barrier</u>: energy gap between the best and worst conformation when you go through a full 360° rotation (as would take place in a full bond rotation)

• Draw in Entergy diagram:



Conformations of Butane and Longer Alkanes (3.8)

CH₃CH₂-CH₂CH₃ is more complex. Focus down C2-C3 bond.

• Online students, watch: <u>https://www.youtube.com/watch?v=xXci5VGousQ</u>



Questions

- 1. Draw the energy diagram
- 2. What would be the rotation barrier?

Strain Energy Factors:

- 1. <u>Torsional</u> strain (why all of the eclipsed type conformations are worse). Repulsion between bonded electrons
- 2. <u>Steric</u> strain: When atoms themselves get too close. Atom-atom repulsion.
- 3. <u>Angle</u> strain: When bond angles can't achieve ideal VSEPR angles. (No angle strain in ethane or butane)

Total Strain =	Torsional strain (are any bonds eclipsed?)
	+ Steric strain (are any atoms too close)
	+ Angle strain (are any bond angles forced to be other than ideal?)

Questions

- 1. In general, why are staggered better than eclipsed?
- 2. Why is eclipsed better than totally eclipsed?
- 3. Why is anti better than gauche?
- 4. Why is gauche better than eclipsed?
- 5. Why is anti better than totally eclipsed?

Chem 350 Jasperse Ch. 3 Notes

Summary

- 1. Anti < gauche < eclipsed < totally eclipsed
- 2. Steric and torsional reasons
- 3. The bulkier a substituent, the greater the steric strain in eclipsed and totally eclipsed conformations

Skills. Be Able to:

- 1. predict relative rotation barriers
- 2. write a conformational analysis (rotation/energy diagram)
- 3. draw Newman pictures for any bond in any structure
- 4. identify anti/gauche/eclipsed/totally eclipsed conformations

Steps to Drawing Newman Structure:

- 4. Draw a circle (back carbon) with a dot in the middle
- 5. Add three sticks extending from the periphery of the circle, with one of them straight up
- 6. Add three sticks extending from the center dot (front carbon) to illustrate the bonds radiating from the front carbon

$$\bigcirc \longrightarrow H^{\operatorname{CH_3}}_{\operatorname{H}} \longrightarrow H^{\operatorname{CH_3}}_{\operatorname{H}} \xrightarrow{\operatorname{CH_3}}_{\operatorname{H}} \xrightarrow{\operatorname{CH_3}}_{\operatorname{CH_3}}$$

Problems

5. Rank the rotation barriers for the following, relative to the indicated bonds



6. Draw Newman projections for the best and worst conformations of the structure shown, relative to the indicated bond. Use the 3^{rd} carbon in the back.

Chem 350 Jasperse Ch. 3 Notes

<u>Higher Alkanes</u> -for any alkane, anti conformations best = zig-zag layout

<u>3.10 Cycloalkanes</u> Nomenclature: cyclopropane, cyclobutane, etc..

General formula: C_NH_{2N} -this is also true for cycloalkanes with chain(s) attached

3.11 Substituted Cycloalkanes and cis/trans Isomers in Disubstituted Cycloalkanes Nomenclature:

- Monosubstituted: alkylcycloalkane
- Disubstituted: cis- (or trans-)-x-alkyl-y-alkylcycloalkane
 - 1. "Cis"-same side "trans" opposite sides
 - 2. Number ring so as to minimize numbers

	Total Ring	Strain	Main
	Strain	Per	Source
Ring Size	(kcal/mol)	CH_2	Of Strain
3	28	9	Angle Strain
4	26	7	Angle Strain
5	7	1	Torsional Strain (eclipsing)
6	0	0	STRAIN FREE
7	6	1	Torsional Strain (eclipsing)
8	10	1	Torsional Strain (eclipsing)

<u>Ring Stability and Ring Strain (3.12)</u>

Structural Isomer Problems (3.2, 3.10)

- <u>Check formula first</u>. Is it an acyclic molecule (C_NH_{2N+2}) , or not? (C_NH_{2N}) could be a cyclic alkane, or perhaps an alkene ...)
- <u>**Be systematic**</u>. Try the longest possible chain (or largest ring size) first, then systematically shorten it and find the branched isomers.
- Avoid duplicates!
- Beware of things that look different but are really the same thing.
- 1. Draw all structural isomers of C₇H₁₆. (Be systematic; no duplicates!)

2. Draw all structural isomers of C₇H₁₄. (Be systematic; no duplicates!)
Cyclohexane Chair Conformations (3.13)

- 1. Cyclohexane has no angle strain or torsional strain
- 2. Cyclohexane has perfect 109° angles with staggered, non-eclipsed C-C bonds
- 3. Obviously it is not flat (natural angle for a flat cyclohexane would be 120°)

Chair Conformations:



- 1. Chairs A and B are constantly interconverting via "boat" E
- Online students: watch <u>https://www.youtube.com/watch?v=6VUU- JExMs</u>
- 2. A and **B** are best to draw and work with.
- 3. But C/D make it easier to visualize why it's called a "chair": 4 carbons make the seat of the chair, one makes backrest, one a footrest.

Process for Drawing Both Chairs:



- 1. Draw a 4-carbon zig-zag. It helps if your left-most carbon is a little lower than your 3rd carbon
- 2. Add a 5th carbon and 6th carbon, but don't have them exactly underneath the 2nd and 3rd carbons.
- 3. Connect the 6th carbon to the orginal 1st carbon
 - For a "left-handed chair", start up and zig-zag down.

"Axial" and "Equatorial" Positions for Substituents



- 1. Each carbon has one axial and one equatorial H's
- 2. Always have six axial attachments
- 3. 3 axials up (on alternating carbons)
- 4. 3 axials down (on alternating carbons)

Chem 350 Jasperse Ch. 3 Notes

- 5. Always have six equatorial attachments
- 6. For processing cis/trans problems, it's helpful to recognize "upper" from "downer" positions
- 7. When a chair flips, what was equatorial becomes axial, and what was axial becomes equatorial
- Online students: (same one as last page) watch <u>https://www.youtube.com/watch?v=6VUU-_JExMs</u>



Drawing equatorial and axial bonds:

- Make axial straight up or straight down (3 each)
- Make equatorial bond lines almost exactly horizontal
- Equatorials are easiest to draw on left and right-most carbons

Drawing Mono- and DiSubstituted Cyclohexanes (Sections 3-14,15)

• Always attach the first substituent onto the leftmost carbon (easiest to draw)



- Draw in the H on any substituted carbon, but skip on H-only carbons
- Equatorial is better than axial for steric reasons. In the axial configuration, the substituent has destabilizing steric interactions
 - Online students, watch: <u>https://www.youtube.com/watch?v=R9VkDTjgd_w&list=PLAhRiX8pHhMK15f</u> <u>WwZQvZmBpPAv2LMVFQ</u>
 - 2 extra gauche interactions, and 1,3-diaxial interactions
- For disubstituted chairs, let the cis/trans relationship guide whether the second substituent should be in an "upper" or "lower" position relative to the original substituent.
- If one substituent is bigger than the other, the most stable chair will always have the larger substituent equatorial

Questions:

- 1. Draw both chair forms for cis-1-isopropyl-2-methylcyclohexane.
- 2. Which is the best chair for cis-1-isopropyl-2-methylcyclohexane?
- 3. Draw both chair forms and identify the best chair for trans-1-isopropyl-2methylcyclohexane.
- 4. Which is more stable, cis- or trans-1-isopropyl-2-methylcyclohexane?
- 5. Then answer the same questions for the 1,3- and 1,4- isomers.





Ch. 4 The Study of Chemical Reactions

<u>Three Factors in Every Reaction</u>: (4.1)

- 1. Mechanism: what is the step-by-step pathway by which old bonds break and new bonds form?
- 2. Thermodynamics: what are the energy changes, both for the overall reaction and for individual steps in the reaction mechanism?
- 3. Kinetics: How fast does a reaction occur? How do changes in reactant structure, reaction solvent, or reaction temperature speed up or slow down a reaction?

The Chlorination of Methane: A Case Study (4.2)



Observations

-usually a mixture of products forms, including not only mono-chlorinated product **A**, but also polychlorinated products **B-D**.

- 4. Light (or heat) is required to initiate the reaction (energy required)
- 5. Blue light, absorbed by Cl₂, is most effective
- 6. High "quantum yield": one photon can result in conversion of thousands of methane reactant molecules into product molecules
 - Q: if light energy is needed, why isn't one photon needed for each reaction?

ANY MECHANISM MUST BE CONSISTENT WITH EXPERIMENTAL OBSERVATIONS

The Mechanism: Radical Chain Reaction (4.3)

Balanced Reaction: $CH_4 + Cl_2 \xrightarrow{hv} CH_3Cl + HCl$

The mechanism must show all bonds broken and made:

Bonds Broken	Bonds Made

3 Phases in Mechanism

- 1. Initiation (gets it started)
- 2. Propagation (keeps on going and going and going)
- 3. Termination (what happens when it sometimes stops)

Initiation

$$Cl_{J}$$
 Cl_{J} C

• In a radical initiation step, two reactive radicals form from a nonradical precursor

PROPAGATION



- 1. In each propagation step, one reactive radical reacts with a nonradical to produce a new reactive radical and a new nonradical.
- 2. Since a reactive radical is reproduced in each step, you always have another reactive radical ready to keep the chain going.
- 3. The chlorine radical produced in step two acts as reactant in step 1.
- 4. Thus you can sustain a repeating chain of step 1- step 2 step 1- step 2 step 1 step 2 step 1 step 2 step 1 step 2 step 1 step 2 etc.
 - As long as there is a radical around, the chain will keep going/propagating
- 5. The sum of the two propagation steps is the overall balanced reaction

Termination



Mechanism Notes:

- 1. "<u>**Radical**</u>" = Something with an unpaired electron.
 - Radicals never satisfy octet rule \rightarrow <u>highly unstable</u> and <u>highly reactive</u>.
- 2. <u>Initiation</u> is needed to initially generate <u>radicals</u>. But once you've got some, radicals subsequently reproduce so that initiation isn't required any more.

3. <u>The main action is the propagation phase. Memorize how that works.</u>

- The propagation phase involves a repeating chain of events (step 1 step 2 step 1 step 2 etc.) that continuously regenerate radicals and continuously convert reactants to products. "Chain reaction"
- 5. The overall reaction is the sum of the two propagation steps. Notice that the methyl and chlorine radicals cancels themselves out, but the products and reactants don't.
 - The carbon radical produced in step one is consumed in step 2
 - The chlorine radical produced in step two is consumed in step 1



- 6. Like initiation, termination occurs only occasionally. This is in part because the concentration of radicals is really small, so it's improbable that they will collide.
 - If you have two radicals and a mole of methane and chlorine, is a radical more likely to collide with another radical or a neutral?
- 7. Notice:
 - Initiation: one nonradical in \rightarrow two radicals out
 - <u>Each Propagation Step:</u> radical + nonradical → nonradical + radical
 - Any Termination Step: radical + radical \rightarrow one nonradical

Free Energy, Enthalpy, Entropy (4.4, 4.5)

 $\Delta G = \Delta H - T \Delta S$

- ΔG : Free Energy: favorable reactions have negative ΔG
- Δ H: Enthalpy: heat lost or gained
 - $\Delta H < 0$ exothermic $\Delta H > 0$ endothermic
- ΔS : Entropy: degree of randomness, disorder

In organic, enthalpy almost always dominates Exothermic → Favorable Endothermic → Unfavorable

If you can figure out whether a reaction will be exothermic or not, you can tell whether it is energetically favorable or not.

• But, being energetically favorable still doesn't prove it will happen very fast... That's the kinetics issue, see later...

Bond Energies: (4.6)

- Exothermic reactions break weaker bonds and form stronger bonds
- Exothermic steps (in a multistep reaction) also trade weaker for stronger
- Extensive tables of bond energies are available (Table 4.3) for when bonds break in half (to give two radicals)
- Often relative bond energies can be predicted by inspection

Bond Strength	Bond Energy (kcal/mol)	Molecule	Products	Radical Stability

$$\begin{array}{c} H \longrightarrow F \rightarrow \\ H \longrightarrow Cl \rightarrow \\ H \longrightarrow Br \rightarrow \\ H \longrightarrow I \rightarrow \end{array}$$

Skills:

- 1. Given bond energies, be able to rank bond strengths
- 2. Given bond energies, be able to rank radical stabilities
- 3. Given known radical stabilities, be able to predict relative bond strengths
- 4. Memorize the stability pattern for the halogen radicals
- 5. Memorize the bond strength pattern for H-X bonds
- 6. <u>Memorize: C-X bonds have the same pattern: iodide is the weakest</u>

H ₃ C—F	H ₃ C—Cl	H ₃ C—Br	H ₃ C—I
109	84	70	56

• Just as acidity reflects <u>anion</u> stability, bond energy values reflect <u>radical</u> <u>stability</u>

Why are H-F and C-F bonds stronger than H-I and C-I bonds?

- 1. <u>Electronegativity and radical stability: (Remember)</u>
 - a. Radicals are short of octet rule \rightarrow electron poor
 - b. The more electronegative fluorine is least willing to be electron poor. As you go down the table, electronegativity decreases and it's less problematic to become radical
- 2. Atomic size and orbital overlap:
 - Fluorine is small, and it's orbitals match up well size-wise with H and C resulting in strong overlap and strong bonds.
 - Iodine is big, so it's orbitals don't match up well or overlap so well with H or C resulting in weak bonds.

Problems:

- 1. H₃C—SeH bonds are weaker than H₃C—OH bonds. Which is more stable, •SeH or •OH?
- 2. Which is stronger, CH3CH2—Cl or CH3CH2—Br?
- 3. Problem: Rank the probable stability of the following radicals, 1 being most stable and 4 being least stable? (Use electronegativity to guide you...)

H₃C• H₂N• HO• F•

Two Types of Bond Breaking and Mechanistic Arrow Pushing:

Heterolysis: one atom keeps both electrons (usual case)

- a. Ions are involved
- b. Arrow-pushing involves double-barbed arrows (~)



Homolysis: Bond breaks in half so that an electron goes with each atom (rare, but that's the type in this chapter)

- 1. Radicals are involved
- 2. Arrow-pushing involves single-barbed arrows (____)

$$(CI \bullet H - CH_3 - F + H - CI$$

One electron in C-H bond goes off with carbon. The other stays with Hydrogen, and matches up with the electron from chlorine to make the new H-Cl bond.

Using Bond Energies to Calculate Energy Changes (4.7)

 $\Delta H =$ (bond energies of bonds broken) - (bond energies of bonds formed)



Q1: What is Δ H:

Q2: Is the overall reaction energetically favorable?

Notes:

- 1. Compare the energies of the bonds broken versus the bonds made
- 2. For an energetically **favorable** process, <u>weaker bonds are replaced by</u> <u>stronger bonds</u>
- 3. With known bond energies, you can quantitatively calculate ΔH
- 4. Even without bond energy numbers, a qualitative sense of bond strengths enables evaluation of whether or not a reaction makes sense energetically
- 5. This type of analysis can be applied both to overall reactions, but also for individual steps in a multi-step reaction.



Q1: Which step is better?

Q2: Which step is likely to be the rate-limiting step?

Q3: Note: Can you see what initiation would cost, and why a good chunk of energy is required to make it happen?

Kinetics, Reaction Rates, and Rate Laws (Gen Chem Review) (4.8)

- 1. Lots of reactions with seemingly favorable ΔH energetics don't happen very fast or at all
- 2. We're often really interested in reaction speed ("kinetics"). Not so simple!
- 3. Rate Law: relationship between reactant concentrations and overall rate

General rate law: rate = k[A]^x[B]^y

- 1. k is rate constant: each reaction has it's own unique rate constant.
- 2. We will often be able to make qualitative predictions based on structural factors
- 3. "x" and "y" are the "orders" of reactants A and B
- 4. the "overall order" of a reaction = x + y
- 5. Shown below are key S_N2 and S_N1 substitution reactions from chapter 8



Notes

a. Different rate laws reflect different mechanisms

- b. Reactants that do not appear in a rate law do not appear in the mechanism until after the rate determining step
- c. The "k" values for the two reactions are **not** the same.
- d. Concentrations matter, for reactants that appear in the rate law
- e. Concentrations reflect not only how many moles of reactant are available, but also the amount of solvent.

Solvent impact: Rates are impacted not only by the amount of reactants but also by the amount of solvent. When you dilute a reactant, the reaction slows due to reduced collision frequency. The impact depends on the rate law and overall order.

Q1: If you use the same number of moles of reactants in reaction one above involving bromobutane **A** above, but you triple the volume of solvent, how much will the rate change?

Q2: If you triple the volume of solvent for reaction two involving 2-bromo-2-methylpentance C, again without changing the number of moles of reactants, how much will the rate change?

Activation Energies and Dependence of Rates on Temp (Gen Chem Review) (4.9)

- So, if every reaction has it's own rate law and it's own k value, what influences the "k" value?
- Arrhenius Equation: $k = Ae^{-Ea/RT}$
 - A is a constant
 - <u>Ea or Eact is the "activation energy"</u>
 - R is the ideal gas constant
 - <u>T is the temperature</u>

Practical Stuff. k-values (and thus rates) are impacted by:

1. <u>Temperature:</u>

- a. Higher temp \rightarrow higher k \rightarrow faster reaction
- b. Lower temp \rightarrow smaller k \rightarrow slower reaction
- c. Crude guide: for every 10° rise in temp, the k value and reaction rate will double for an ordinary reaction. (This is super, super, super crude, though...)

2. Activation Energy of Activation or Activation Barrier, Eact

a. It's the minimum energy required to cross the energy barrier between reactants and products

b. The height of the barrier influences reaction speed.

- c. Activation barriers explain why many exothermic, energy-favorable reactions don't actually occur at room temperature
- d. Temperature reflects the average kinetic energy of the molecules; but some are always above average.
 - a. An increase in temperature can strongly increase the reaction rate because a small temperature increase can substantially increase the population of molecules with E_{act}



Reaction Progress for a Simple, One-Step Mechanism

Transition States (4.10)



Reaction Progress for a Simple, One-Step Mechanism

• The transition state is the <u>highest, worst energy spot</u> on the road from reactants to products

Since rates are affected by E_{act} , and E_{act} 's are determined by Transition States, \rightarrow Transition states influence reactions rates.

- Lower transition state \rightarrow faster reaction
- Higher transition state \rightarrow slower reaction
- Why are T-states usually higher in energy than either products or reactants? And why do reaction with very favorable ΔH often have fairly high T-states?
 - Because one full bond is better than two partial bonds. At the T-state, you are routinely at the transition between a breaking bond and a forming bond.



Three Stability/Reactivity Principles

- 1. <u>Transition-State Stability/Reactivity Principle</u>: The <u>more stable the transition state</u>, the <u>faster the reaction</u> will be.
- 2. <u>Reactant Stability/Reactivity Principle: The more stable the reactant, the slower it reacts</u>
 - A more stable reactant has lower starting energy. Therefore it has a larger E_{act} to get over the transition state.
 - A less stable reactant has a higher starting energy, is closer to the T-state, and thus has a smaller energy barrier to cross.
- 3. <u>Product Stability/Reactivity Principle:</u> The more stable the product, the faster it forms.
 - A more stable product has lower energy. Often the T-state is stabilized/lowered by the same structural factors that stabilize the products.

Rates of Multistep Reactions (more Gen Chem Review) (4.11)



Reaction Progress for a Simple, Two-Step Mechanism

- 1. Most reactions involve 2 or more steps with one or more "intermediates" (•CH₃ for example)
 - An "<u>intermediate</u>" is something that forms temporarily, but then rapidly converts into something else. Normally the intermediate is highly reactive, has a short lifetime, and never builds up.
 - There is only one transition state for the overall process, no matter how many steps
 - The <u>transition state</u> for the overall reaction is still the <u>highest, worst energy spot</u> on the road from reactants to products
 - The step that goes through the transition state will be the <u>slowest step</u> and is referred to as <u>the rate-determining step</u> or the <u>slow step</u>.

Practical: To handle rates, identify and focus on the slowest step!!!

<u>Practical Identification</u>: The rate determining step is **always** the step leading to the least stable intermediate. (ex: \cdot CH₃ is less stable than \cdot Cl)

- Therefore the ability to recognize stability patterns for reactive intermediate radicals, cations, and anions is super useful
- 2. The Crucial Link Between "Slow Step" Identification and Application of Stability/Reactivity Principles
 - In a multistep reaction, <u>the reactants and products that matter kinetically are the</u> <u>reactants and products of the slow step</u>. Which are often reactive intermediates.
 - To apply the <u>**Product Stability/Reactivity Principle**</u>, (which says that <u>more stable the</u> <u>product</u>, the <u>faster the reaction</u>), you need to:
 - Know the mechanism. (What is the rate determining step? And what kind of reactive intermediate is produced in that rate-determining step?)
 - Know how structural factors impact the relative stabilities of reactive intermediates. (For example, is a 3° radical better or worse than a 1° radical?)
 - To apply the <u>Reactant Stability/Reactivity Principle</u>, (which says that <u>more stable</u> <u>the reactant</u>, the <u>slower the reaction</u>), you need to:
 - Know the mechanism. (What is the rate determining step?)
 - Know how structural factors impact the relative stabilities of a reactive intermediates. (For example, is Cl• more or less stable than Br•?)

Dependence of Halogenation Rates on Halogen (4.12)

General reaction: $CH_4 + X_2 \rightarrow CH_3X + HX$

Rate determining step: $CH_4 + \bullet X \rightarrow \bullet CH_3 + HX$

			Eact	•X	•X
	<u>Halogen</u>	Rate Determining Step	(kcal/mol)	Stability	Reactivity
Useless	F_2	$CH_4 + \bullet F \rightarrow \bullet CH_3 + HF$	1		
Useful	Cl ₂	$CH_4 + \bullet Cl \rightarrow \bullet CH_3 + HCl$	4		
Most Useful	Br ₂	$CH_4 + \bullet Br \rightarrow \bullet CH_3 + HBr$	18		
Useless	I ₂	$CH_4 + \bullet I \rightarrow \bullet CH_3 + HI$	34		

• Iodine is not reactive enough; fluorine is actually too dangerous to use

Applying the Reactant Stability/Reactivity Principle: The more stable the reactant, the slower it will react.

• Since the halogen radicals are reactants in the rate determining step, and since fluorine radical is least stable and iodine radical is most stable => reactivity is $F \cdot > Cl \cdot > Br \cdot > I \cdot$, and => reactivity is $F_2 > Cl_2 > Br_2 > I_2$

<u>Selective Halogenations of Higher Alkanes (Higher than Methane) (4.13,14)</u>

- This is where most of the real problems will come from
- A. Chlorination of Propane

$$H_2$$
 H_2 $H_3C^{-}C_{-}C_3$ $+ Cl_2$ $H_3C^{-}C_{-}C_3$

Notes

Why are 2° C-H's more reactive than 1° C-H's?

- Think rate determining step
- Which stability/reactivity principle should you apply, and how?

$$H_{2}$$

$$H_{3}C^{-C}CH_{3}$$

$$+ Cl \cdot Path 1^{\circ}$$

$$Path 2^{\circ}$$

$$2^{\circ} radical$$

Path 2° is faster than path 1° because path 2° produces a more stable radical product. The path 2° transition-state is stabilized as a result. Product stability/reactivity principle.

B. Free Radical Stability Pattern: $3^{\circ} > 2^{\circ} > 1^{\circ} > methyl$

Memorize!

R	R R-C• >		H H-C
R-C• > R	H H	H H	H-C• H
3°	2°	1°	methyl



- 1. Resonance helps a lot ("<u>Allylic</u>")
- 2. Being on an alkene is bad ("<u>Vinylic</u>")

	CH ₂	C, H	H CH_	CH ₂ H	H−CH ₃	CH H
Bond	87	91	95	98	104	111
Energy						
Class	Allylic	3°	2°	1°	Methyl	vinyl

C. Bromination of Propane



Notes

- 1. Bromine is <u>way</u> more selective than chlorine
- 2. Practical: to do a selective halogenation, use bromine rather than chlorine
- 3. Just as $2^{\circ} > 1^{\circ}$, so ally lic $> 3^{\circ} > 2^{\circ} > 1^{\circ} >$ methyl > vinyl

D. Why bromination is more selective than chlorination:

Reactant Stability/Reactivity/Selectivity Principle:

- 1. Review: When a reaction can give two products, the pathway leading to the more stable product will be preferred (product stability/reactivity principle).
- 2. New: the <u>selectivity</u> between formation of the more stable and less stable product <u>will</u> <u>vary depending on the stability of the reactant</u>.
 - In the propane example, propane is a reactant and the two competing products are the secondary and primary radicals, regardless of whether bromine or chlorine is used. But the differing stability/reactivity profiles of the bromine versus chlorine radicals is key
- 3. The <u>more stable the reactant</u>, the <u>less reactive</u> it will be and the <u>more selective it will be</u> <u>for the more stable product</u>.
- 4. A more stable reactant is less desperate to react, and is more choosy for the best path/product.
 - "Beggars can't be choosers": less stable reactant (the beggar) is less choosy/selective
 - More sophisticated: a more stable reactant has larger activation barriers to cross. It has trouble crossing even the lower activation barrier to the best product, and rarely has the energy to cross the higher barrier to the less stable product. A less stable reactant has more energy and can more easily cross the barriers to either product.

Application to the Propane Halogenation Situation:

- Br• is more stable than Cl•,
- Therefore Br• is more selective and choosy to make the better 2° radical (leading to 2bromopropane) rather than the less stable 1° radical (leading to 1-bromopropane).
- Cl• is less stable, and really wants to react. So it doesn't wait around for a weak 2° hydrogen; it often settles for a stronger 1° hydrogen even though it gives an inferior1° radical product (in the rate determining step)
- "<u>Beggars can't be choosers</u>": the less stable, more reactive Cl• is the "beggar" than can't be as choosy as the more stable, less reactive Br•



Alkane Brominations: Where many of the problems will come Skills:

- 1. Write the mechanism for chain propagation (with detailed arrows)
- 2. Identify all possible monosubstituted products
- 3. <u>Identify the Major Product</u>
 - Consider all possible radicals. The carbon that gives the most stable radical will be the carbon that gets brominated preferentially.
 - This is true because the rate determining step is the step in which a hydrogen is abstracted and a carbon radical is formed.
 - Thus, according to the product stability/reactivity principle, the pathway leading via the best carbon radical is the preferred path.
- 1. Do all three things for:

$$+ Br_2 \xrightarrow{hv}$$

Mechanism

2. Identify the Major Product for each of the following:



<u>Reactive Intermediates: Stability Patterns (</u>4.16)

- 1. Shortlived, unstable, highly reactive intermediates
- 2. Normally lack normal bonding

These are tremendously important:

- 1. They will be the <u>least stable intermediate</u> in any multistep mechanism
- 2. When formed, they are **products of the rate-determining step**
- 3. Factors that stabilize them will speed up reaction rates

Thus it is very important to know their stability patterns!

Class	Structure	Stability Pattern		
Carbocations	C⊕	Allylic > 3° > 2° > 1° > methyl > alkenyl (vinyl, aryl)	Electron Poor	Electrophilic/ Acidic
Carbon Radicals		Allylic > 3° > 2° > 1° > methyl > alkenyl (vinyl, aryl)	Electron Poor	Electrophilic/ Acidic
Carbanions	-c:	Allylic > alkenyl (vinyl, aryl) > methyl > 1° > 2° > 3°	Electron Rich	Nucleophilic/ Basic

<u>Notes</u>

- 1. Both carbocations and radicals have the same pattern. So you don't need to memorize them twice!
- 2. Carbanions are almost exactly the reverse, except that being allylic is ideal for both.
- 3. All benefit from resonance (allylic).
- 4. Cations and radicals both fall short of octet rule. As a result, they are both electron deficient. Carbanions, by contrast, are electron rich.
- 5. Alkyl substituents are electron donors. As a result, they are good for electron deficient cations and radicals $(3^{\circ} > 2^{\circ} > 1^{\circ} > \text{methyl})$ but bad for carbanions.
- 6. Alkenyl (vinyl or aryl) carbons are inherently a bit electron poor. This is excellent for carbanions, but terrible for cations or radicals.

Stability/Reactivity/Selectivity Principles

<u>Reactant Stability/Reactivity</u>: The more stable the reactant, the less reactive it will be.

- In terms of rates, this means that the more stable the reactant, the slower it will react.
- The concept here is that the more stable the reactant, the more content it is to stay as is, and the less motivated it is to react and change into something different
- <u>Key note:</u> Often the "reactant" that's relevant in this context will not be the original reactant of the reaction, but will be the "reactant" involved in the rate determining step.
 - So you need to both figure out what the mechanism is and know what structural factors will stabilize or destabilize the reactants.

1. Basicity



Why: As anion stability increases from A to D, the reactivity decreases

2. Nucleophilicity



3. Nucleophilicity



Why: As anion stability increases from A to D, the reactivity decreases

4. Reactivity toward alkanes via radical halogenation

 $F_2 > Cl_2 > Br_2 > l_2$ because $F_{\bullet} > Cl_{\bullet} > Br_{\bullet} > l_{\bullet}$

Why: Chlorine is more reactive the bromine because chlorine radical is less stable then bromine radical.

5. Electrophilicity (Reactivity in S_N2, S_N1, E2, E1 Reactions)

Why: As carbon-halogen bond stability increases, the reactivity decreases

Product Stability/Reactivity: The more stable the product, the faster it will form.

- **a.** In terms of rates, this means that the <u>more stable the product</u>, the faster the reaction.
- **b.** The concept here is that the more stable the product, the more favorable it will be to make that product.
- **c.** <u>Key note:</u> Often the "product" that's relevant in this context will not be the final product of the reaction, but will be the "product" of the rate determining step.
 - 1. So you need to both figure out what the mechanism is and know what structural factors will stabilize or destabilize the products.
- 1. Acidity

$$\bigcirc$$
 CH₃ < \bigcirc NH₂ < \bigcirc OH < \bigcirc OH

Why: Because as the stability of the anion products increases from A to D, the reaction gets faster = the reactivity of the parent acid increases



3. S_N1, E1 Reactivity (see Ch. 8, test 2)



Why: Because as the stability of the cation produced in the ratedetermining step increases, the reaction gets faster



Transition-State Stability/Reactivity: The more stable the transition state, the <u>faster</u> the reaction will be. (The concept here is that the lower the transition state, the more easily it will be crossed.)

• S_N2 Reactivity (ch. 8)



Why: The pattern reflects the relative stability of the transition states. In the case of 3° versus 2° versus 1°, the issue is steric congestion in the transition state. The transition states for the more highly substituted halides are destabilized. In the case of allylic halides, the transition state is stabilized for orbital reasons, not steric reasons.

<u>Reactant Stability/Reactivity/Selectivity</u>: Often a reaction can proceed to give either of two products, of unequal stability. The pathway leading to the more stable product will be preferred. However, the selectivity between formation of the more stable and less stable product will vary depending on the stability of the reactant. The <u>more stable the reactant</u>, the <u>less reactive</u> it will be and the <u>more selective it will be</u>. (The concept here is that a more stable reactant is less desperate to react, and is more choosy, better able to select the best possible pathway without using a less favorable pathway that would result in a less stable product. A more sophisticated picture is that a more stable reactant will have larger activation barriers to cross; it has a hard enough time crossing even the lowest transition state leading to the best possible product, and is much less likely to have the surplus energy required to cross the high transition state leading to the less stable product.)

Key note: The "reactant" and "products" involved are those for the rate-determing step.

1. Selectivity in the reaction of bromine versus chlorine with alkanes via radical halogenation



Ch. 5 Stereochemistry

- Stereoisomers have the same condensed formulas and basic bonding sequence, but have different 3-dimensional shape and cannot be interconverted
- Online students: watch <u>https://www.youtube.com/watch?v=UX5lwbnAAcw</u>

Chirality (5.2)

chiral-equivalent to "handed". A molecule is chiral if it is not superimposable on its mirror image.

achiral- A molecule is achiral if it is the same as its mirror image.

enantiomers-Two molecules that are mirror images of each other but are different and are not superimposable on each other.

- Note: "enantiomers" involves a relationship between two structures.
- "Chiral" is a term that applies to a single molecule.

<u>Drawing Mirrors/Enantiomers:</u> <u>Exchange of any two attachments</u> inverts the stereochemistry and produces a mirror image of the original:

- 1. front and back (hashes and wedges)
- 2. left and right (while keeping your hashed and wedged attachments unchanged)
- 3. exchanging a left or right with the hashed position in back



chiral carbon (or stereocenter or asymmetric carbon atom or chirality center)-an atom bearing groups such that interchange of 2 of the groups produces a stereoisomer.

1. Any tetrahedral atom that has four different attached groups is a chiral carbon.

<u>Recognizing Chiral Molecules</u>: Key is to look for chiral carbons/stereocenters

- 1. <u>zero</u> chiral carbons \rightarrow molecule is <u>achiral</u>
- 2. <u>one</u> chiral carbon \rightarrow molecule is chiral
- 3. If <u>two</u> (or more) chiral carbons \rightarrow molecule may be <u>chiral or achiral</u>
 - <u>no plane of symmetry</u> under any conditions \rightarrow <u>chiral</u>.
 - <u>yes plane of symmetry</u> (in one conformation or drawing perspective) \rightarrow <u>achiral</u>
 - a. if a molecule has ≥ 2 chiral carbons but has a plane of symmetry such that it is achiral, it is called a **meso** compound
 - b. to recognize whether a molecule with ≥2 chiral carbons is achiral or chiral, try to draw it in a way such that the carbons are maximally symmetrical, so that it will be easiest to see whether or not a plane of symmetry exists. This may sometimes involve using a sawhorse rather than a zig-zag picture to maximize the ease of seeing potential symmetry.

1. Classify as Chiral or Achiral



2. What is the Relationship Between the Following Pairs of Structures. Are they the same, or enantiomers?



3. Identify each stereocenter with an asterisk, then classify the configuration of each stereocenter as (R) or (S). (Can do the same with the structures in problems 1 and 2)



<u>R/S Classification for Chiral Carbons (</u>5.3)

- 1. <u>Assign Priority</u> of Atoms/Groups attached to a tetrahedral stereocenter (1 highest, 4 lowest)
 - a. <u>Element</u>: An element with higher atomic number has higher priority
 - Halogen > Oxygen > Nitrogen > Carbon > Hydrogen
 - b. <u>Carbon with attached heteroatom</u> > carbon without any attached heteroatom
 - c. <u>CH > CH₂ > CH₃</u> for carbons with no heteroatoms
- 2. In case of carbon versus carbon ties, differentiate at nearest point of difference.
 - If you have to walk down the chain to find a difference, do it one carbon at a time
- a. $CH_2OH > CH_2CH_3$ b. $CH_2OCH_3 > CH_2NH_2$ c. $C(=O)CH_3 > CH(OH)CH_3$
- d. $CH(CH_3)_2 > CH_2CH_2CH_2CH_3$ e. $CH(CH3)_2 > CH_2C(=O)CH_3$ f. $CH_2NH_2 > CH(CH_3)CO_2H$
- g. $CH=CH_2>CH_2CH_2CH_2CH_3$ h. $CH=CH_2>CH(CH3)_2$ i. $CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_3$
- 3. Double or triple bonds are treated as if each of the bonds has extra C's attached. Rules 1b and 1c above still hold as usual.



- 4. If the low priority group 4 (normally H) is in the back (hashed), trace a path from $1 \rightarrow 2 \rightarrow 3$.
 - If the path goes <u>clockwise</u>, the stereocenter is (R)
 - If the path goes <u>counterclockwise</u>, the stereocenter is (S)
- 5. If the low priority group 4 (normally H) is in front (wedged), then the situation is reversed.
 - If the path goes clockwise, the stereocenter is (S)
 - If the path goes counterclockwise, the stereocenter is (R)
- 6. If the low priority group 4 (normally H) is to the left or to the right, redraw by exchanging it with the group in the back (hashed), and trace the path on the resulting figure. The configuration in the original structure will be the opposite from in the redrawn structure.
 - If the path in the redrawn picture goes <u>clockwise (R)</u>, the original stereocenter is (S)
 - If the path in the redrawn picture goes <u>counterclockwise</u>(S), the original was (R)

<u>Drawing Structure, Given Name</u>: Draw the easiest one, with H in back. If correct, great! If incorrect, simply redraw with the H in front.

Ex: Draw (R)-3-chloroheptane

Enantiomers and How They Differ (5.4,5) **Enantiomers have indistinguishable properties in most ways:**

- 1. Melting points
- 2. Boiling points
- 3. Solubility
- 4. Density
- 5. Chemical reactivity towards <u>achiral</u> reactants.

Enantiomers Differ in only Two Ways

- 1. Reactivity with <u>Chiral Chemicals</u> (Major chemistry difference)
 - Enzymes are like left-handed gloves, which routinely select left-handed over righthanded enantiomers
 - An achiral molecule is like a mitten that fits a left hand or right hand equally well.

Chiral reactants discriminate between enantiomers and react with one faster than the other

Achiral reactants do not discriminate between enantiomers and react equally with either one

2. Optical Activity: Enantiomers Rotate the Plane of Polarized Light in Opposite Directions (5.4) (Major Diagnostic difference)

- <u>"Optically Active"</u>: A <u>solution</u> is optically active if it rotates polarized light
- Enantiomers rotate light in equal but opposite directions
- <u>"Optically Inactive"</u>: A <u>solution</u> is optically inactive if it does not rotate light
- Note: optical activity is a property of a bulk solution, not an individual molecule
- A bulk solution is optically active if it has an excess of one enantiomer

Two Ways to Be Optically Inactive

- If the solution has no chiral molecules present, or
- If the solution has a 50/50 mixture of chiral enantiomers (a "racemic mixture")
- Note: "optically active" indicates the presence of chiral molecules, but "optically inactive" does <u>not</u> prove the absence of chiral molecules! It only means that there is no excess of one enantiomer over the other!
- Q: Classify each of the following as "optically active" or "optically inactive"
- 1. A solution of 1-bromopropane.
- 2. A solution with equal quantities of (R)-2-bromobutane and (S)-2-bromobutane
- 3. A solution of pure (R)-2-bromobutane
- 4. A solution with 80% (R)-2-bromobutane and 20% (S)-2-bromobutane
- 5. If pure (R)-2-bromobutane rotates light 100° to the right, what would happen to light applied to pure (S)-2-bromobutane?
- 6. If pure (R)-2-bromobutane rotates light 100° to the right, how much rotation would occur for a solution with 80% (R)-2-bromobutane and 20% (S)-2-bromobutane

<u>Racemic Mixtures</u> (5.6)

- Racemic mixture-a solution containing an equimolar, 50/50 mixture of enantiomers.
 - A racemic mixture is optically inactive.
 - It will not rotate light because the enantiomers cancel each other out.
 - But a racemic mixture is still "chiral".
 - Other aliases: racemic, racemic mix, racemate, a (\pm) pair, a (d,l) pair
- The vast majority of solutions containing chiral molecules are racemic.
- 7. Most reactions that produce chiral molecules provide a racemic, 50/50 mixture of enantiomers



8. For chiral molecules, assume a racemic mixture unless told otherwise



5.6 Enantiomeric Excess ("ee") and Optical Purity

- enantiomeric excess (ee) = [(mole fraction major enantiomer)-(mole fraction minor enantiomer)] x 100
- **optical purity** = [observed rotation/rotation of pure enantiomer] x 100
- Note: Enantiomeric excess and optical purity values are exactly the same, but are used depending on the experimental method of measurement. Enantiomeric excess is used when you determine the mole/mole ratio of enantiomers by NMR or some other method; optical purity is used when you use optical rotation to characterize a solution containing a mixture of enantiomers.

Problem: A solution has 80% (R)-2-bromobutane and 20% (S)-2-bromobutane

- 1. What is the "enantiomeric excess" of (R)-2-bromobutane?
- 2. If pure (R)-2-bromobutane rotates light 100° to the right, how much rotation would occur for a solution with 80% (R)-2-bromobutane and 20% (S)-2-bromobutane
- 3. If a solution has a 50/50 mixture of (R)- and (S)-2-bromobutane, what would be the enantiomeric excess and the optical purity?
- 4. If a solution has a 50% ee, what would be the ratio of enantiomers?
 - a. 50% R, 50% S or
 - b. 75% R, 25% S

<u>Chirality and Conformations</u> (5.8)

• Avoid conformational pictures, which may deceptively give the appearance of chirality

If any conformation or drawing of a molecule has a symmetry plane, it is achiral



Freaks: Chiral Compounds without Chiral Carbons: Not Tested. (5.9)

- 1. There are some molecules that don't have a tetrahedral chiral carbon but are still chiral.
- 2. As with any chiral "handed" object, they must left/right and front/back differences and lack symmetry.
- 3. One case is allenes (shown)
- 4. Another is when two aromatics are connected to each other, sit perpendicular, and can't rotate for steric reasons.



Ex: Allenes

Fischer Projections: (5.10). Not Tested Now. A Fischer Projection Handout is included on the website (http://www.mnstate.edu/jasperse/), for future reference.

Diastereomers: Cis/Trans Stereoisomers that are **Not** Enantiomers. (5.11)

• Online students: watch the following. Diastereomer discussion begins just before 5minute mark: <u>https://www.youtube.com/watch?v=UX5lwbnAAcw</u>



- Note: for acyclics you can rotate around and have different looks for the same molecule, depending on whether you're eclipsed or zig-zagged relative to the single bonds.
- Be consistent. If you zig-zag one, zig-zag the other. If you eclipse one, eclipse the other.
- Normally, for stereo questions, the zig-zag layout isn't conducive to recognizing symmetry.
- So for stereo questions, the more symmetric eclipsed layout is preferable
- Non-test note: Cis or trans is unambiguous for alkenes and rings, but not for acyclics. Often "syn" or "anti" is used instead, assuming the zig-zag layout.



Summary: Types of Isomers

Molecules with ≥2 Chiral Carbons (5.12)

- 1. <u>Rule: The maximum number of potential stereoisomers = 2^n (n = number of chiral carbons)</u>
- 2. Remember: If a molecule can be drawn with a plane of symmetry, then it is achiral and it's mirror image will be the same as the original.
- 3. If one possible isomer is achiral, then you won't get the maximum number of unique stereoisomers because two of them will be identical mirror images
- 4. <u>Suggestion: Try to draw molecules so as to maximize symmetry, regardless of actual conformational stability. This may often involve drawing an eclipsed picture rather than zig-zag</u>

Problem:

- Draw all unique stereoisomers of 2-bromo-3-chlorobutane.
- Identify each picture with a Letter (A, B, etc.), and then specify the relationships between each pair as either same, enantiomers, or diastereomers.
- Identify each picture as chiral or achiral (meso)

Meso Compounds (5.12)

- Online students: watch the following. Meso discussion begins just before 7-minute mark: <u>https://www.youtube.com/watch?v=UX5lwbnAAcw</u>
- **meso compound**-an achiral, optically inactive molecule that contains tetrahedral stereocenters (usually two). Both of the Br-bearing carbons in cis-1,2-dibromocyclopentane are stereocenters, but the molecule itself has a plane of symmetry and is achiral.



- a. Remember: If a molecule can be drawn with a plane of symmetry, then it is achiral and it's mirror image will be the same as the original.
- b. Meso compounds always involve 2 (or more) chiral carbons. Never just one.
- c. When a meso structure is involved, you won't get the maximum 2ⁿth number of stereocenters
- d. <u>Suggestion: Try to draw molecules so as to maximize symmetry, regardless of actual conformational stability. This may often involve drawing an eclipsed picture rather than zig-zag</u>
- e. <u>A meso compound will not have an enantiomer</u>
- f. To draw an enantiomer, invert <u>all</u> hash/wedges (but be sure you're chiral to begin with)
- **g.** To draw a diastereomer, invert one but not both hash/wedges
- 1. Problem:
 - a. Draw all unique stereoisomers of 2,3-dibromobutane.
 - b. Identify each picture with a Letter (A, B, etc.), and then specify the relationships between each pair as either same, enantiomers, or diastereomers.
 - c. Identify each picture as chiral or achiral (meso)

2. Draw all unique stereoisomers of 2,3-dibromopentane. Identify each picture with a Letter (A, B, etc.), and then specify the relationships between each pair as either same, enantiomers, or diastereomers. Identify each picture as chiral or achiral (meso)

3. Draw all unique stereoisomers of 2,4-dibromopentane. Identify each picture with a Letter (A, B, etc.), and then specify the relationships between each pair as either same, enantiomers, or diastereomers. Identify each picture as chiral or achiral (meso)

4. Draw all unique stereoisomers of 1,3-dibromocyclopentane. Identify each picture with a Letter (A, B, etc.), and then specify the relationships between each pair as either same, enantiomers, or diastereomers. Identify each picture as chiral or achiral (meso)

5. Identify each picture as chiral or meso



Absolute and Relative Configuration (5.14)

Absolute: (R) or (S)

Relative: Comparison between 2 molecules or 2 chiral carbons (even if we don't know absolute)

Br NaOH S _N 2 reaction Inversion	$\begin{array}{c} H_{3}C, Br \\ H_{2}O \\ S_{N}1 \text{ reaction} \\ \text{Racemization} \end{array} H_{3}C, OH \\ H$
	$\bigcup_{\text{cis}} \stackrel{\text{OH}}{\longrightarrow} \stackrel{\text{OsO}_4}{\xrightarrow{H_2O_2}} \stackrel{\text{HCO}_3\text{H}}{\longrightarrow} \stackrel{\text{HCO}_3\text{H}}{\xrightarrow{H_2O}} \stackrel{\text{OH}}{\xrightarrow{H_2O}} \stackrel{\text{OH}}{\stackrel$

• Relative stereochemistry is often an important feature in mechanisms and product predictions

Diastereomers Differ in Physical Properties (Unlike Enantiomers) (5.15)

• Diastereomers have different melting points, boiling points, solubilities, etc. (unlike enantiomers)

$$Br Br Br Br HO_2C CO_2H HO_2C CO_2H mp = 158 mp = 273$$

Separation of Enantiomers via Diastereomers (5.16)

• Enantiomers can be separated by temporary attachment to an optically active thing \rightarrow resulting in separable diastereomers \rightarrow chop attachment following separation



Chem 350 Chapter 5 Stereochemical Terminology Summary

Terms and Definitions

Classification of Isomers

isomers-different compounds with the same molecular formula.

structural isomers (or constitutional isomers)-isomers that have their atoms connected in a different order.



stereoisomers (or configurational isomers)-isomers in which atoms are joined in the same order but differ in the way their atoms are arranged in space. Stereoisomers are subdivided into two categories: enantiomers and diastereomers.

conformations-easily interconverted by σ -bond rotation or cyclohexane chair flips. In butane, for example, the gauche, eclipsed, and staggered forms are considered to be different **conformations**; in cyclohexanes, the two chairs are conformations. <u>Different conformations</u> are not considered stereoisomers.



Summary: Types of Isomers



Classification of Stereoisomers

enantiomers-stereoisomers that are not superposable on their mirror reflections. Ex. (R)-2-bromobutane and (S)-2-bromobutane. Separate enantiomers rotate polarized light and are said to be <u>optically active</u>.



diastereomers-stereoisomers that are not enantiomers, that is, not mirror images of each other. Ex. cis- and trans-2-butene; cis- and trans-1,3-dimethylcyclopentane; (2R)-(3R)-2-bromo-3-chlorobutane and (2R)-(3S)-2-bromo-3-chlorobutane. Diastereomers are cis/trans-type isomers, although isomers such as those drawn below are sometimes called syn/anti instead. If the carbon skeletons are drawn analogously, two molecules whose hash/wedge attachments have a cis-trans type relationship will be diastereomers.



Miscellaneous Stereochemical Terms

chiral-equivalent to "handed". A molecule is chiral if it is not superimposable on its mirror image; an achiral molecule is superimposable on its mirror image.

chiral carbon (or stereocenter or asymmetric carbon atom)-an atom bearing groups such that interchange of 2 of the groups produces a stereoisomer. <u>Any tetrahedral atom that has four different attached groups is a chiral carbon.</u>

• Most molecules containing tetrahedral stereocenters are chiral (the exception being "meso compounds".) The configuration of a tetrahedral stereocenter can be designated as (R) or (S).

configuration-the particular arrangement of atoms in space that is characteristic of a given stereoisomer. The configuration of each stereocenter can be designated as (R) or (S).

racemic mixture-a 50/50 mixture of two enantiomers that will not rotate light.

meso compound-an achiral, optically inactive molecule that contains tetrahedral stereocenters (usually two). Both of the Br-bearing carbons in cis-1,2-dibromocyclopentane are stereocenters, but the molecule itself has a plane of symmetry and is achiral.



meso, has stereocenters but is achiral due to plane of symmetry

R/S Classification for Chiral Carbons

- 5. Assign Priority of Atoms/Groups attached to a tetrahedral stereocenter (1 highest, 4 lowest)
 - a. For different elements, higher atomic number takes priority
 - Halogen > Oxygen > Nitrogen > Carbon > Hydrogen
 - b. In case of carbon versus carbon ties: Differentiate at nearest point of difference
 - 1. A carbon with a heteroatom attached beats one without
 - 2. For carbons with no heteroatoms, one with more H's loses to one with less
 - 3° carbon > 2° carbon > 1° carbon > CH_3
 - c. Handling double bonds and triple bonds
 - A carbon with more H's again loses to one with fewer
 - Double or triple bonds are treated as if each of the bonds has extra C's attached



- 6. If the low priority group 4 (normally H) is in the back (hashed), trace a path from 1→ 2 → 3.
 - d. If the path goes <u>clockwise</u>, the stereocenter is (R)
 - e. If the path goes <u>counterclockwise</u>, the stereocenter is (S)
- 7. If the low priority group 4 (normally H) is in front (wedged), then the situation is reversed.
 - f. If the path goes <u>clockwise</u>, the stereocenter is (S)
 - g. If the path goes <u>counterclockwise</u>, the stereocenter is (R)
- 8. If the low priority group 4 (normally H) is to the left or to the right, exchange it with the group in the back (hashed), and trace the path on the resulting figure.
 - h. If the path goes <u>clockwise</u>, the stereocenter is (S)
 - i. If the path goes <u>counterclockwise</u>, the stereocenter is (R)
- 9. In Fisher projections, since H is always in front, clockwise is (S) and counterclockwise is (R)
<u>Drawing Mirrors/Enantiomers</u>: Exchange of any two attachments inverts the stereochemistry and produces a mirror image of the original:

- 1. front and back (hashes and wedges)
- 2. left and right (while keeping your hashed and wedged attachments unchanged)
- 3. flipping something on a side (could be the left side or the right side) with the hashed position in back



<u>Recognizing Chiral Molecules</u>: Key is to look for chiral carbons/stereocenters

- 1. If <u>zero</u> chiral carbons \rightarrow molecule is <u>achiral</u>
- 2. If <u>one</u> chiral carbons \rightarrow molecule is **chiral**
- 3. If <u>two</u> (or more) chiral carbons \rightarrow molecule may be <u>chiral or achiral</u>
 - a. if it has <u>no plane of symmetry</u> under any conditions, it is <u>chiral</u>.
 - b. If it has <u>a plane of symmetry</u> (in one conformation or drawing perspective), then it is <u>achiral</u>
 - c. if a molecule has ≥ 2 chiral carbons but is achiral with a plane of symmetry, it is called a <u>meso</u> compound
 - d. to recognize whether a molecule with ≥2 chiral carbons is achiral or chiral, try to draw it in a way such that the carbons are maximally symmetrical, so that it will be easiest to see whether or not a plane of symmetry exists. This may sometimes involve using a sawhorse rather than a zig-zag picture to maximize the ease of seeing potential symmetry.

Terminology Related to Enantiomeric Purity

enantiomeric excess (ee) = [(mole fraction major enantiomer)-(mole fraction minor enantiomer)] x 100

optical purity = [observed rotation/rotation of pure enantiomer] x 100

Note: Enantiomeric excess and optical purity values are exactly the same, but are used depending on the experimental method of measurement. Enantiomeric excess is used when you determine the mole/mole ratio of enantiomers by NMR or some other method; optical purity is used when you use optical rotation to characterize a solution containing a mixture of enantiomers.

racemic mixture-an equimolar mixture of enantiomers. A racemic mixture will not rotate light.

Fischer Projections

In Fischer projections, atoms attached to horizontal lines are viewed as being in front of the plane (wedged), and atoms attached to vertical lines are viewed as being behind the plane (wedged). In the following pictures, Et=ethyl, Me=methyl.



The two structures shown above are enantiomers



The two shown here are diastereomers.



The two shown here are not stereoisomers; they are "meso compounds", because there is a plane of symmetry.

Chem 350 Jasperse Ch. 6 1. Radical Halogenation (Ch. 4) Summary of Reaction Types, Ch. 4-6, Test 2

$$\square$$
 Br_2, hv \square Br

resonance stabilized>3°>2°>1°>alkenyl

Recognition: X₂, hv

<u>Predicting product:</u> Identify which carbon could give the most stable radical, and substitute a Br for an H on that carbon.

Stereochemistry: Leads to racemic, due to achiral radical intermediate.

Mech: Radical. Be able to draw propagation steps.



2. S_N2 Substitution

Recognition:

$$Br$$
 NaOCH₃ OCH ₃ S_N ^{2: 1°>2°>3°> alkenyl}

Any of a large variety of nuclophiles or electrophiles can work.

A. Anionic Nucleophile, and

B. 1° or 2° alkyl halide

 $(3^{\circ} alkyl halides fail, will give E2 upon treatment with Anionic Nucleophile/Base. For 2° alkyl halides, S_N2 is often accompanied by variable amounts of E2.)$

Predicting product: Replace the halide with the anion nucleophile

Stereochemistry: Leads to Inversion of Configuration

Mech: Be able to draw completely. Only one concerted step!



3. E2 Reactions.



Recognition:

A. Anionic Nucleophile/Base, and B. 3° or 2° alkyl halide

(1° alkyl halides undergo S_N2 instead. For 2° alkyl halides, E2 is often accompanied by variable amounts of S_N2 .)

Orientation: The most substituted alkene forms (unless a bulky base is used, ch. 7)

<u>Predicting product:</u> Remove halide and a hydrogen from the neighboring carbon that can give the most highly substituted alkene. The hydrogen on the neighboring carbon must be trans, however.

<u>Stereochemistry</u>: Anti/trans elimination. The hydrogen on the neighbor carbon must be trans/anti.

Mech: Concerted. Uses anion. Be able to draw completely. Only one concerted step!

4. S_N1 Reactions.



<u>Recognition</u>: A. Neutral, weak nucleophile. No anionic nucleophile/base, and B. 3° or 2° alkyl halide. (Controlled by cation stability).

(1° alkyl halides undergo S_N2 instead. For 2° alkyl halides, S_N1 is often accompanied by variable amounts of E1.)

<u>Predicting product:</u> Remove halide and replace it with the nucleophile (minus an H atom!) <u>Stereochemistry</u>: Racemization. The achiral cation intermediate forgets any stereochem. <u>Mech</u>: Stepwise, 3 steps, via carbocation. Be able to draw completely.



5. E1 Reactions. $3^{\circ} > 2^{\circ} > 1^{\circ}$ (Controlled by cation stability)



<u>Recognition</u>: A. Neutral, weak nucleophile. No anionic nucleophile/base, and B. 3° or 2° alkyl halide. (Controlled by cation stability).

(For 2° alkyl halides, E1 is often accompanied by variable amounts of S_N1.)

Orientation: The most substituted alkene forms

<u>Predicting the major product:</u> Remove halide and a hydrogen from the neighboring carbon that can give the most highly substituted alkene. The hydrogen on the neighboring carbon can be cis or trans.

Stereochemistry: Not an issue. The eliminating hydrogen can be cis or trans. .

Mech: Stepwise, 2 steps, via carbocation. Be able to draw completely.



Sorting among $S_N 2$, $S_N 1$, E2, E1: How do I predict? Step 1: Check nucleophile/<u>base</u>.

- If **neutral**, then $S_N 1/E1 \rightarrow$ mixture of both
- If anionic, then $\overline{S_N 2/E2}$.

Step 2: If anionic, and in the SN2/E2, then Check the substrate.

- $\circ 1^{\circ} \rightarrow \underline{S_{N2}}$
 - $2^{\circ} \rightarrow \overline{S_N 2} / E2$ mixture. Often more $S_N 2$, but not reliable...
 - $\circ \quad 3^{\circ} \rightarrow \underline{\mathbf{E2}}$

Ch. 6 Alkyl Halides: Nucleophilic Substitution and Elimination

<u>Classification, Nomenclature (</u>6.1,2)

A. General Classification

"alkyl halide"	
"vinyl halide"	
"aryl halide"	
"allylic halide"	

B. 1°, 2°, 3° Classification



C. Systematic Naming: x-Haloalkane (test responsible) (Include number!)

D. Common Naming: "alkyl halide" (not tested)

Structure	Formal Name	Common Name
Br		
		Isopropyl iodide

Systematic Nomenclature: x-Haloalkane (test responsible) Common: "alkyl halide" (not tested)

Uses:

- 1. solvents
- 2. anesthetics
- 3. refrigerants
- 4. pesticides
- 5. reactants

<u>Structure</u>: (6.4)

A. Polar	C δ_{+} δ_{-}	

B. Weak Bonds, Breakable

Stability	Bond	Bond Strength	Reactivity Toward Breakage
	C-Cl	81	
	C-Br	68	
	C-I	53	

<u>Physical Properties.</u>(6.5)

- boiling point: controlled by molecular weight (London force)
- water solubility: low, no hydrogen-bonding
- density: greater than water, so they sink (unlike hydrocarbons, which float)

Preparation of Alkyl Halides (6.6)

- Review: $R-H + Br_2 \rightarrow RBr + HBr$ (under photolysis, Ch. 4)
- We will learn other preparations in chapters 8 and 11

<u>Overview/Preview of Alkyl Halide Reactions:</u> Substitution ($S_N 2$ or $S_N 1$) or Elimination (E2 or E1) (6.7)

- Because R-X bonds are weak, halides are good leaving groups.
- E. Substitution

R-X + NaZ or $HZ \rightarrow R-Z + NaX$ or HXAnion or neutral

- 2 Variants
- 6. S_N2:
 - Anionic nucleophile
 - The R-X bond breaking is simultaneous with R-Z bond formation

$$\bigcirc Br \xrightarrow{\bigcirc} OCH_3 \longrightarrow OCH_3 + Br \xrightarrow{\bigcirc} S_N^{2: 1^{\circ}>2^{\circ}>3^{\circ}> \text{ alkenyl}}$$

- 7. S_N1:
 - Neutral nucleophile
 - The R-X bond breaks first to give a carbocation in the rate determining step; formation of the R-Z bond comes later



F. Elimination



2 Variants

- 1. E2:
 - Anionic base
 - The R-X and C-H bond breaking is simultaneous with C=C bond formation



- 2. E1:
 - Neutral base
 - The R-X bond breaks first to give a carbocation in the rate determining step.
 C-H bond cleavage and C=C bond formation comes later



The S_N2 Reaction (6.8)



Example, with test-level mechanism:

NaOH
$$H_3C \xrightarrow{\frown} Br \longrightarrow HO \xrightarrow{\frown} CH_3 + NaX^{\ominus}$$

- double-barbed arrows (electron pairs move)
- Na⁺ is a spectator

More Detailed Mechanism:



Notes:

- 1. Simple, concerted one-step mechanism. No intermediates.
- 2. The anion needs to be very reactive and thus not too stable. Normally <u>ANIONIC</u> <u>NUCLEOPHILE</u>.
- 3. Both nucleophile and electrophile are involved in the rate determining step.
 - Rate = $k[anion]^{1}[R-X]^{1}$
- 4. 2^{nd} order rate law is why it's called $S_N 2$: <u>Substitution_Nucleophilic</u> and order
- 5. The nucleophile attacks opposite side from the leaving group.
- 6. This "backside attack" (or opposite side attack) results in inversion of stereochemistry when a chiral, 2° R-X is involved

 $\frac{H}{M} \frac{Br}{F} + NaOH \longrightarrow \frac{HO}{M} \frac{H}{F}$ Inversion of Stereochemistry at Chiral Center

- 7. The <u>transition state</u> involves a 5-bonded, trigonal bipyramidal carbon that <u>is more</u> <u>cluttered</u> than either the original tetrahedral reactant or the final tetrahedral product
- 8. Steric crowding in the transition-state makes the reaction very, very, very sensitive to steric factors
 - a. For the electrophile R-X: $CH_3-X > 1^{\circ} R-X > 2^{\circ} R-X > 3^{\circ} R-X$ for steric reasons
 - b. For the nucleophile it also helps to be smaller rather than larger

Generality of S_N2 Reactions. (6.9)

-many kinds of nucleophiles, give many products

1. $R-X + NaOH \rightarrow R-OH$ Alcohols2. $R-X + NaOR \rightarrow R-O-R$ Ethers3. $R-X + NaOR \rightarrow R \rightarrow R \rightarrow R \rightarrow R$ Esters4. $R-X + KI \rightarrow R-I$ Iodides5. $R-X + NaCN \rightarrow R-CN$ Nitriles6. $R-X + \Theta = -R \rightarrow R \rightarrow R - R$ Alkynes

Etc.

Notes

- 1. Most nucleophiles are ANIONS
- 2. Various oxygen anions are good to make alcohols, ethers, or esters
- 3. Halogen exchange useful route to iodides (more valuable and less accessible)
- 4. There are a few neutral nucleophiles (not for test): nitrogen family

Predicting Products for S_N2 Reactions

- 1. Don't change the structure for the carbon skeleton
- 2. <u>Put the nucleophile in exactly the spot where the halide began...</u>
- 3. Unless the halide was attached to a <u>chiral</u> center; in that case invert the configuration for the product
 - If the halide was "wedged", the nucleophile should be "hashed"
 - If the halide was "hashed", the nucleophile should be "wedged"
- 4. Don't mess with any "spectator" portions: whatever was attached to the nucleophilic anion at the beginning should still be attached at the end

Structural Factors that Impact S_N2 (6.10, 6.11)

A. Nucleophile

- 1. Anion versus Neutral: Should be ANIONIC
- 2. Anion Stability: Less Stable should be More Reactive (Reactant Stability-Reactivity Principle)
 - a. -anion nucleophilicity <u>decreases</u> across a <u>horizontal row</u> (electronegativity factor)

b. -anion nucleophilicity <u>decreases</u> when an anion is stabilized by <u>resonance</u>

c. -anion nucleophilicity increases down a vertical column

NaSeH > NaSH > NaOH

3. Size: all else equal, smaller is better than bigger

Ma > Mona

B. Electrophile

- 1. <u>Substrate: Allylic > 1° > 2° > >> 3°</u>, alkenyl, aryl
 - <u>3° and alkenyl, aryl never do S_N2</u>
 - transition-state stability-reactivity principle
 - Steric clutter in the transition state explains the $1^{\circ} > 2^{\circ} > >> 3^{\circ}$ pattern
 - Allylic benefits from a complex orbital resonance effect in the T-state
 - Alkenyl/aryl halides are bad for some molecular orbital reasons (backside attack doesn't work, particularly for aryl halides)

2. <u>Leaving Group: R-I > R-Br > R-Cl</u>

- reactant stability-reactivity principle
- weaker bonds break faster

Inversion of Stereochem in S_N2 (6.12)

In the mechanism, the nucleophile attacks from the "backside" or opposite side from the leaving group \rightarrow inverts configuration



- Inversion occurs mechanistically in every S_N2_reaction
- But inversion is chemically relevant **only** when a chiral carbon is involved

$$\begin{array}{c|c} Br & H & & H & OCH_3 \\ \hline & & & & & & \\ \hline & & & & & & \\ \hline Inversion matters, since product is chiral & Inversion doesn't matter, for achiral product \\ \hline \end{array}$$

Predicting products when chiral carbons undergo inversion:

- 1. Keep the carbon skeleton fixed
- 2. If leaving group is "hashed", the nucleophile will end up "wedged" in the product
- 3. If leaving group is "wedged", the nucleophile will end up "hashed" in the product

$$\begin{array}{c} & \underbrace{\text{NaOCH}_2\text{CH}_3}_{\text{Br}} \\ & \underbrace{\text{Br}}_{\text{H}} \\ & \underbrace{\text{H}}_{3}\text{C} \\ & \underbrace{\text{H}}_{1} \\ & \underbrace{\text{Cis}} \end{array}$$

Two Standard Proofs for S_N2 mechanism:

- Inversion of configuration on a chiral carbon
- 2nd order rate law

Predicting Products for S_N2 Reactions

- 1. Don't change the structure for the carbon skeleton
- 2. <u>Put the nucleophile in exactly the spot where the halide began...</u>
- 3. Unless the halide was attached to a <u>chiral</u> center; in that case invert the configuration for the product
 - a. If the halide was "wedged", the nucleophile should be "hashed"
 - b. If the halide was "hashed", the nucleophile should be "wedged"
- 4. Don't mess with any "spectator" portions: whatever was attached to the nucleophilic anion at the beginning should still be attached at the end

S_N2 Problems: For each of the following

- a. Identify whether or not an S_N 2 reaction would take place?
- b. If not, why not?
- c. For those that could undergo $S_N 2$ substitution, draw in the product.



More S_N2 Problems

1. Rank the reactivity toward NaOCH₃ (For any problem like this, try to recognize what kind of a reaction it is, so that you know what stability/reactivity issues apply).

Issues:

2. Rank Reactivity toward Br (For any problem like this, try to recognize what kind of a reaction it is, so that you know what stability/reactivity issues apply).

NaNH ₂	NaOCH ₃	NaO	CH₃OH

Issues:

3. What nucleophile should you use to accomplish the following transformations?



4. Draw the Products, Including Stereochemistry. (Stereochemistry will matter for $S_N 2$ and $S_N 1$ reactions anytime the haloalkane is 2°)



Issue:

5. Choose Reactants to make the following, from a haloalkane and some nucleophile.



Issues:

<u>**S**N1 = Substitution_{Nucleophilic}1st Order = "Solvolysis"</u> (6.13)

• Dramatic difference in mechanism, rates, structure dependence, and stereochemical outcome (compared to $S_N 2$)

General:
$$R-X + Z-H \rightarrow R-X + HX$$

neutral

Neutral, non-anionic nucleophiles do the substitution

- 1. Often this is just the solvent (H₂O, ROH, RCO₂H are common)
 - For this reasons, these reactions are often called "solvolysis" reactions
- 2. Heat is often required
- 3. Acid is sometimes used to accelerate S_N1 reactions

Predicting Products for S_N1 Reactions

- 1. Don't change the structure for the carbon skeleton
- 2. Connect "R" and "Z", while taking the halide off of the electrophile and H off of the nucleophile
- 3. Unless the halide was attached to a <u>chiral</u> center, a <u>racemic mixture</u> will result
- 4. Maintain the integrity of the spectator attachments

Examples:

$$\rightarrow$$
 \dot{CI} + H₂O \rightarrow

3-Step Mechanism



1. Step 1: Carbocation Formation. THIS IS THE SLOW STEP

• Therefore the rate is controlled by cation stability!

- 2. Step 2: Carbocation capture by neutral molecule (usually a solvent molecule)
 - When cation and neutral combine, a cation is produced
- 3. Step 3: Deprotonation to get neutral

Notes:

- 1. Carbocation formation is key
- 2. Rate = $k[R-X] \rightarrow First order$
- 3. See cations, not anions. Neutral, not anionic nucleophile.
- 4. Charge and atoms must balance in step 2. Thus, the oxygen retains the hydrogen.
- 5. Oxygen eventually loses the H, but only in step 3.
- 6. Rate can be enhanced by AgNO₃. The Ag+ cation helps strip the halide off in step 1.

<u>Structural</u> Factors that Impact $S_N 1$ Rates

Nucleophile: Should be NEUTRAL, but otherwise non-factor

Electrophile

- 1. Substrate: Allylic $> 3^{\circ} > 2^{\circ} > > 1^{\circ} >$ alkenyl, aryl
 - Resonance is huge
 - \circ alkenyl, aryl never do S_N2, 1° only with AgNO₃
 - product stability-reactivity principle: in the rate-determining step, the more stable the product <u>cation</u>, the faster it will form
 - \circ In terms of 1°, 2°, 3°, S_N1 and S_N2 have exactly opposite patterns
- 2. Leaving Group: R-I > R-Br > R-Cl
 - reactant stability-reactivity principle: in the rate determining step, the weaker the C-X bond, the faster it will break
 - \circ This pattern is the same as for $S_{\rm N}2$

3. AgNO₃ Helps

- Ag+ helps strip the halide off in step one
- 4. Polar Solvent Helps
 - A polar solvent helps to stabilize the ions that form in the rate-determining step

Solvent Polarity:					
Solvent	H ₂ O	CH3OH	o≓	<u> </u>	\sim
Relative Rate	8000	1000	1	0.001	0.0001

<u>S_N1 Stereo: Racemization.</u>(6.14)

Original stereochemistry is forgotten at the carbocation stage, get racemic R/S mixture



Why? Carbocation forgets original stereo:



<u>S_N1 Problems</u>: For the following, which <u>are and aren't</u> S_N1 candidates? If not, why not? What would be the product if they are S_N1 candidates?



Comparing S_N2 vs S_N1 (6.16)

		<u>S_N1</u>	<u>S_N2</u>
1	Nucleophile	Neutral, weak	Anionic, strong
2	Substrate	3° R-X > 2° R-X	1° R-X > 2° R-X
	Allylic effect	Allylic Helps	Allylic helps
3	Leaving Group	I > Br > C1	I > Br > Cl
4	Solvent	Polar needed	Non-factor
5	Rate Law	K[RX]	k[RX][Anion]
6	Stereochemistry	Racemization	Inversion
	(on chiral, normally 2° R-X)		
7	Ions	Cationic	Anionic
8	Rearrangements	Problem at times	Never

Identify as S_N1 or S_N2 or No Reaction. Draw the Product(s), if a reaction occurs.

1.
$$\longrightarrow$$
 Br + NaOCH₂CH₃ \longrightarrow





Which fit S_N1, which fit S_N2?

- 1. Faster in presence of silver nitrate?
- 2. Faster in water than in hexane?
- 3. When the moles of reactant is kept the same, but the volume of solvent is cut in half, the reaction rate increases by 2-fold?
- 4. By 4-fold?
- 5. 2-bromobutane reacts faster than 1-bromobutane?
- 6. 2-bromobutane reacts slower than 1-bromobutane?

E1 Elimination Reactions (7.9,10)

Examples:



Notes

- Under S_N1 conditions, some elimination product(s) form as well
- E1 and S_N1 normally compete, resulting in mixtures
 - This is not good from a synthetic perspective.
- Structurally Isomeric Alkenes can form
 - The double bond must involve the original halogenated carbon and any neighbor carbon (that had a hydrogen to begin with that can be eliminated)
 Normally the alkene with fewer alkene H's is formed more extensively over
 - alkenes with more alkene H's. (More C-substituted alkene is major).
- Neutral/acidic (the formula starts neutral, but acid is produced)
- 1^{st} order rate law $r = k[RX]^1$

E1 Mechanism: 2 Steps



- 1. Step 1: Carbocation Formation. THIS IS THE SLOW STEP
 - a. Therefore the rate is controlled by cation stability! Just like $S_N 1!$
 - b. Benefits from exactly the same factors that speed up S_N1 (3° > 2°, RI > RBr, polar solvent, etc..)
- Step 2: Deprotonation from a carbon that neighbors the cation/original halogenated carbon

 Can draw bromide as base for simplicity
 - b. But often it's actually water or alcohol solvent that picks up the proton

E1 Summary

<u>Recognition</u>: A. Neutral, weak nucleophile. No anionic nucleophile/base, and B. 3° or 2° alkyl halide. (Controlled by cation stability).

(For 2° alkyl halides, E1 is often accompanied by variable amounts of $S_{N}1$.)

Orientation: The most substituted alkene forms

<u>Predicting the major product:</u> Remove halide and a hydrogen from the neighboring carbon that can give the most highly substituted alkene. The hydrogen on the neighboring carbon can be cis or trans.

Stereochemistry: Not an issue. The eliminating hydrogen can be cis or trans. .

Mech: Stepwise, 2 steps, via carbocation. Be able to draw completely.



E2 Reaction (2nd Order, Under Anionic/Basic S_N2 type Conditions) (7-12)

Notes

- E2 happens with anionic nucleophiles/bases, when S_N2 is hindered •
- Structurally Isomeric Alkenes can form •
 - The double bond must involve the original halogenated carbon and any neighbor 0 carbon (that had a hydrogen to begin with that can be eliminated)
 - Normally the alkene with fewer alkene H's is formed more extensively over 0 alkenes with more alkene H's. (More C-substituted alkene is major).

Mech

$$\begin{array}{c} & & \\$$

- anionic. Anion base gets things started.
- 2nd order rate law. Rate = $k[R-X]^{1}$ [anion base]¹
- It all happens in one concerted step, but there are three arrow to show all the bond • making and breaking

Bonds Made	Bonds Broken
Base to hydrogen	C-X bond
C=C pi bond	C-H bond

E2 Summary

<u>Recognition</u>: A. Anionic Nucleophile/Base, and

B. 3° or 2° alkyl halide

(1° alkyl halides undergo S_N2 instead. For 2° alkyl halides, E2 is often accompanied by variable amounts of S_N2 .)

Orientation: The most substituted alkene forms (unless a bulky base is used, ch. 7) **Predicting product:** Remove halide and a hydrogen from the neighboring carbon that can give the most highly substituted alkene. The hydrogen on the neighboring carbon must be trans, however.

<u>Stereochemistry</u>: Anti elimination. The hydrogen on the neighbor carbon must be trans/anti.

<u>Mech:</u> Concerted. Uses anion. Be able to draw completely. Only one concerted step!

 $S_N 1 vs E1$



• Both satisfy the carbocation. They just meet it's bonding need with different electrons.

 $S_N 2 vs E2$



- 1. Both provide an electron pair to displace the C-Br bond pair. They just use different electrons.
- 2. Both involve the anion. It's called the nucleophile in the SN2, the base in the E2.
- 3. The SN2 involves a crowded transition state, and thus is strongly impacted by steric factors. The E2 does not have any steric problems (and in fact alleviates them).
- 4. The difference in steric profile explains why for SN2, $1^{\circ} > 2^{\circ} > 3^{\circ}$, but that for E2, the reactivity of 3° is just fine.

<u>Zaitsev's Rule</u>: When E1 or E2 elimination can give more than 1 structurally isomeric alkene, the more highly Carbon-substituted alkene form will predominate over a less highly carbon-substituted alkene. (7.11)

- a. The fewer H's on the product alkene the better.
 - Every Alkene has four attachments. The fewer of these that are H's, the better.
 - When pictures are drawn in which the H's are not shown, the more highly substituted alkenes turn out to be the best.
- b. Why? Product Stability-Reactivity Rule. Alkenes with more C's and fewer H's attached are more stable.
- c. Alkene Stability is shown below: tetra->tri->di->mono->unsubstituted
 - Why?
 - Alkene carbons are somewhat electron poor due to the inferior overlap of pi bonds. (One carbon doesn't really "get" as much of the other carbon's electron as is the case in a nice sigma bond).
 - Since alkyl groups are electron donors, they stabilize electron-deficient alkene carbons.
 - Analogous to why electron-donating alkyls give the 3° > 2° > 1° stability pattern for cations and radicals



Stereochemistry of E2 Eliminations (7.14)

- 1. For E2 (not for E1) C-H and C-X bonds must be in the same plane (coplanar)
- 2. The halogen and the hydrogen being removed must be <u>trans</u> to each
- 3. Why?
 - a. Due to orbital overlap requirements.
 - b. In the concerted E2 mechanism, the electrons from the hydrogen must essentially come in backside to the leaving halide
 - o just as in backside-attack S_N2 mechanism



4. Sometimes, a molecule will need to single-bond spin into a "trans" conformation to enable a trans-elimination.



5. Eliminations in **Cyclic Compounds** are Often impacted by the Trans Requirement

Comparing E2 vs E1

		<u>E1</u>	<u>E2</u>
1	Nucleophile/Base	Neutral, weak, acidic	Anionic, strong, basic
2	Substrate	3° or 2° RX	3° RX (E2 only) or 2° (E2 and SN2)
	Allylic effect	Allylic Helps	Non-factor
3	Leaving Group	I > Br > Cl	I > Br > Cl
4	Solvent	Polar needed	Non-factor
5	Rate Law	k[RX]	k[RX][Anion]
6	Stereochemistry	Non-selective	Trans requirement
7	Ions	Cationic	Anionic
8	Rearrangements	Problem at times	Never
9	Orientation	Zaitsev's Rule: Prefer	Zaitsev's Rule: Prefer more
		more substituted alkene	Substituted alkene (assuming
			trans requirement permits)

<u>Elimination Problems:</u> Draw the major <u>Elimination</u> Product for the following Reactions. Classify as E1 or E2. (There may be accompanying $S_N 2$ or $S_N 1$ material, but to whatever degree elimination occurs, draw the major product.)



<u>Comparing S_N2 vs S_N1 vs E2 vs E1: How Do I Predict Which</u> <u>Happens When?</u>

Step 1: Check nucleophile/base.

- If <u>neutral</u>, then <u>S_N1/E1</u> \rightarrow mixture of both
- If <u>anionic</u>, then $S_N 2/E2$.

Step 2: If <u>anionic</u>, and in the <u>S_N2/E2</u> pool, then <u>Check the substrate</u>.

- $\circ \ 1^{\circ} \xrightarrow{} \underline{S_N 2}$
- 2° → <u>S_N2/E2 mixture.</u> Often more <u>S_N2</u>, but not reliable...
 3° → <u>E2</u>

Notes:

1º R-X	S _N 2 only	No E2 or $S_N1/E1$ (cation too lousy for $S_N1/E1$; S_N2 too fast for E2 to compete)
3° R-X	E2 (anionic) or S _N 1/E1 (neutral/acidic)	No S _N 2 (sterics too lousy)
2° R-X	mixtures common	



- Note: Aryl and Vinyl Halides will not undergo <u>any</u> of these types of reactions.
- If you see Br₂/hv type recipe, then you're back in the chapter 4 world of radical halogenation

For each mixture,

- a. Classify the Type of Reaction (or "no reaction")
- b. Draw the <u>major</u> product. (Or both a substitution and elim product..)



Design Synthetic Plans for converting the starting materials into the target molecules.

- 1. In each case, more than one chemical operation will be required.
- 2. Strategy: R-H → R-Br (via bromination) → Substitution product (via SN2) or alkene (via E2)



Keys:

- 1. These can't be done directly, in a single recipe. At least two laboratory operations are required.
- 2. Each sequence show above requires an increase in functional groups. An S_N2/S_N1 or E2/E1 changes functionality but does not create functionality. But radical bromination does create a functional group.
- 3. Thus the key reaction for creating the functionality: $R-H \rightarrow$
- 4. Once you've converted the starting alkane to alkyl bromide, you can interconvert that bromide group into something else by S_N2/S_N1 or E2/E1

Practice: Mechanism Practice

Draw the **mechanism** for formation of the major product in each of the following reactions. In some cases where both elimination and substitution might compete, the problem specifies whether to draw the substitution or elimination mechanism.

1.
1.

$$\begin{array}{c}
 & & \downarrow \\
 & &$$

5.
$$H_2O \xrightarrow{\text{elim}}$$

Practice: Ranking Practice

Rank the Reactivity of the chemicals shown toward the thing in the box. Keys:

- Identify the type of reaction that would be involved
- Think about the rate-determining step and how reactant or product or transition-state stability would influence the rate.



Practice: Predict-the-Product Practice

Give the Major Product(s) for each of the following. If it's likely to give a mixture of both substitution and elimination, just draw the substitution product. Designate stereochemical outcomes when stereochemistry is relevant (2° substrates).

Key: Try to recognize what type of reaction will happen first.



Provide Reactants for the Following (One of the Starting Chemicals must be an R-Br)



Draw the Major Alkene Isomer, Following Elimination



Carbocation Rearrangements (and their impact in S_N1 and E1 reactions) [Tested?] (6.15)

- 1. Carbocations are very unstable, and sometimes rearrange to other more stable carbocations.
- 2. A rearrangement requires that a superior cation will result. Four cases:
 - a. $2^{\circ} \rightarrow \tilde{3}^{\circ}$
 - b. non-allylic \rightarrow allylic
 - c. strained ring \rightarrow unstrained or less strained ring
 - d. 1° cation \rightarrow 2° or 3° cation (rare, since 1° cations are hard to make and pretty rare)



- 3. Two processes for cation rearrangement:
 - a. Hydride shift (an H jumps over)
 - b. Alkyl shift (a carbon jumps over)
 - The resulting cation must always be on a carbon adjacent to the original
 - rearrangement does not occur if you start with a good cation.
- 4. Most cation mechanisms that start with 2° or 3° cations don't undergo rearrangement because rearrangement does not lead to improved cation stability



• Product mixture results from competition between Path A and Path B.





Chapter 7 Reactions and Mechanisms, Review

Ch. 7 Structure and Synthesis of Alkenes

<u>**Review**</u>(7.1,2)

Bond Strength	
C-C σ Bond	83 kcal/mol
C=C π Bond	63 kcal/mol

- π Bonds are much weaker
- π Bonds are thus more breakable and more reactive

Double Bonds can't rotate

Elements of Unsaturation ("EU") (7.3)

- <u>"Saturated Alkane"</u>: C_NH_{2N+2}
- <u>Unsaturated</u> Formula: Has less than the maximum 2N+2 number of hydrogens
- 1. "Element of Unsaturation": Something that reduces the hydrogen count by two
 - a. Double bond
 - b. Ring
- 2. Each element of unsaturation reduces the hydrogen count by two
- 3. A molecule may well have several elements of unsaturation, each one progressively reducing it's hydrogen count by two.

4. Knowing how many elements of unsaturation are present helps to classify, and helps in isomer problems.

5. <u>Calculating EU</u>

General Concept

For Formulas With Nothing Other than C, H, or O

For Formulas That May Include Nitrogen or Halogens

$$EU = \frac{\text{Theory \# H's - Actual \# H's}}{2}$$
$$EU = \frac{(2C + 2) - H}{2}$$

 $\frac{2}{EU = \frac{(2C + 2 + N) - (H + X)}{EU = \frac{(2C + 2 + N) - (H + X)}{EU = \frac{2}{EU = \frac{$

C = # C'sH = # H's

- 6. <u>Heteroatom Effect:</u>
 - Oxygens: No effect
 - Nitrogen: each nitrogen increases the theory # H's by 1
 - Halogen: each halogen takes the place of a hydrogen and reduces the theory # H's by 1.

Calculate how many elements of unsaturation are in the following formulas:

- 2. C5H12
- 3. C4H8
- 4. C3H4O
- 5. C5H9Cl
- 6. C4H11N

Distinguishing Rings from Double Bonds by H₂/Pt Hydrogenation

- a. H_2/Pt will "saturate" <u>all</u> C=C double bonds by adding H_2 across each one.
- b. However, rings will not add hydrogen upon treatment with H₂/Pt
- c. Thus you can count how many of your EU's are rings versus double bonds
- d. Note: 2H's add per 1 double bond



- 7. For C_4H_8 , draw all possible structures for isomer A and isomer B, given the following:
 - a. $C_4H_8(A) \xrightarrow{H_2, Pt} C_4H_{10}$
 - b. C_4H_8 (B) H_2 , Pt \rightarrow No reaction
- 8. Which of the following is possible for structure C?

 C_5H_8 (C) $\xrightarrow{H_2, Pt} C_5H_{10}$



Formulas, EU, and Hydrogenation Test: How to determine the number of alkenes versus rings:

Process

- 1. Determine EU from formula
- 2. Determine alkenes from H2/Pt test
 - 1 alkene per 2H added
- 3. Determine rings by the difference
 - a. EU = alkenes + rings, therefore:
 - b. rings = EU alkenes

Q:	Suppose a	formula is	s C ₇ H ₁₀ ,	how	many EU?	
----	-----------	------------	------------------------------------	-----	----------	--

Given the following H₂/Pt results, how many alkenes and rings would have been in the original formula?

Product after	# of H's		
H_2/Pt	Added	# of Alkenes	# of Rings
A. C ₇ H ₁₂			
B. C ₇ H ₁₄			
C. C ₇ H ₁₆			
D. C ₇ H ₁₀			

Alkene Nomenclature (7.4,5)

A. When the Alkene is in the Core Name (the priority functional group)

- 1. Number the longest continuous alkene-containing C-chain from the end nearest the alkene → core name = "alk-x-ene"
- 2. Designate the position of the alkene by using the lower-numbered of the two alkene carbons
- 3. Attach and number substituents
- 4. When alkene stereoisomer issues apply:
 - Designate stereochemistry as (E) or (Z)

Give formal names for the following alkenes Simple Acyclics





<u>Rings</u>



B. Alkenes as Substitutents

• Many functional groups have higher priority than alkenes, so that alkenes may need to be named as substituents rather than in the core name

Four to Memorize:

$\begin{array}{c c} & H_2 \\ & & & \\ \overset{*}{C} = C \stackrel{H}{\setminus} H \\ H & H \\ & & H \\ \hline \\ Vinyl \\ \end{array} \qquad \begin{array}{c} H_2 \\ & & \\ & \\ & & \\ & & \\ & \\ & & \\ & \\ & & $	=CH ₂ Methylene	Phenyl = "Ph"	
---	-------------------------------	---------------	--

Name the following:


C. E-Z Nomenclature for Alkene Stereochemistry (7.5)

- Nice video explanation, online students: <u>https://www.youtube.com/watch?v=r7giUCU8x_k</u>
- Each carbon of an alkene has two attachments.
- 1. Check whether (E)/(Z) stereochemistry is relevant. If so:
- 2. Identify which of the two attachments on the left alkene carbon has higher priority.
 - Use the same priority rules as were used in R/S chirality context
- 3. Then identify which attachment on the right alkene carbon has higher priority.
- 4. Assign (E) or (Z) based on whether the two priority attachments are on same or opposite side
 - (Z) ("zusammen" = "together"): the priority attachments are cis
 - (E) ("entgegan = "opposite"): the priority attachments are trans



When does (E)/(Z) NOT apply?

• If either alkene carbon has two common attachments, then stereo doesn't apply

Assign as (Z) or (E)





Alkene Stability Pattern (7.8)



- Increasing Substitution (# of non-hydrogens directly attached to alkene carbons) → Increased Stability
 - Why? Electronic Reasons.
 - a. Alkene carbons are somewhat electron poor due to the inferior overlap of pi bonds. (One carbon doesn't really "get" as much of the other carbon's electron as is the case in a nice sigma bond).
 - b. Since alkyl groups are electron donors, they stabilize electron-deficient alkene carbons.
 - c. Analogous to why electron-donating alkyls give the $3^{\circ} > 2^{\circ} > 1^{\circ}$ stability pattern for cations and radicals
- 2. Trans is more stable than cis for 1,2-disubstituted alkenes
 - Why? Steric Reasons
- 3. Measuring Relative Stability of Isomers by Heats of Hydrogenation or Heats of Combustion (6.2)



- When 2 isomers can be converted to a common product, the relative magnitude of ΔH tells which isomer is more stable
- The more heat released, the less stable the isomer. The less heat released, the more stable.
- Heat of combustion works the same way (converts products to common CO₂ and H₂O)



Reaction Progress

1. List the number of non-hydrogen substitutents on each alkene; rank the relative stability; rank by heat of hydrogenation, from 1 (most) to 4 (least)

Stability:

Heat:

2. List the number of non-hydrogen substitutents on each alkene; rank the relative stability; When the following are burned, rank from the largest heat of combustion (1) to the smallest.



Stability:

Heat:

3. Which isomer is more stable, given the indicated heats of hydrogenation?



Physical Properties of Alkenes (7.7)

- Nonpolar
- No hydrogen bonding
 - low boiling
 - Hydrophobic

Synthesis of Alkenes by E2 Elimination of Alkyl Halides (7.11-14)



Factors to Consider

1. <u>3° R-X or 2° R-X</u>

- a. 3° R-X gives E2 with any base
- b. 2° R-X gives largely SN2 with normal anions.
- c. 2° R-X gives largely E2 with a <u>bulky base</u>. E2 prevails over S_N2
 - Because SN2 backside attack is so sterically sensitive, bulky bases have problems doing SN2. Get E2 instead.

2. Base Size: Bulky Base versus Normal Base

a. Normal anions:

- 3° R-X give E2 only, no $S_N 2$
- 2° R-X give predominantly S_N2 rather than E2
- E2 elimiantions proceed with Zaytsev orientation: more-subbed alkene predominates

b. Bulky base.

- 3° R-X gives E2 only, no SN2 .
- 2° R-X gives E2 only, no SN2.

3. E2's proceed via Hofmann orientation: less-subbed alkene predominates

- For steric reasons: base goes after less sterically hindered neighbor hydrogen
- 4. 2 Bulky Bases to Memorize:
 - NEt3 (Triethylamine)
 - KOC(CH3)3 potassium t-butoxide

Bulky Bases: 2 to remember	Normal Bases
	NaOH, KOH, LiOH
NEt ₃ = Neutral but amines are basic anyway	NaOCH ₃ , NaOCH ₂ CH ₃ , NaOCH ₂ CH ₂ CH ₃ KOCH ₃ , KOCH ₂ CH ₃ , KOCH ₂ CH ₂ CH ₃
$KOC(CH_3)_3 = KOCMe_3 = \bigcirc_{O} \begin{array}{c} CH_3 \\ -+CH_3 \\ CH_3 \end{array}$ "potassium t-butoxide"	etc.
Bulky bases are: 1. Good S _N 2 nucleophiles only for 1° R-X 2. Do clean E2 with both 3° R-X and 2° R-X 3. Give Hofmann elimination (less substitued alkene major)	 Normal bases are: 1. Anionic 2. Not especially bulky 3. Good S_N2 nucleophiles for 1° or 2° R-X 4. Only do clean E2 with 3° R-X 5. Give Zaitsev elimination (more substitued alkene preferred)

5. Alkene Orientation: Zaytsev versus Hofmann Elimination

- a. Zaytsev: most subbed alkene
 - The major E2 product involves removal of a hydrogen from the most substituted neighbor carbon
 - This results in a maximally substituted, maximally stable alkene (product stability)
 - Normal-sized bases give predominantly Zaytsev elimination
- b. Hofmann: least subbed alkene
 - The major E2 product involves removal of a hydrogen from the least substituted neighbor carbon
 - This results in a less substituted, less stable alkene
 - Bulky bases give predominantly Hofmann elimination
- c. Why: Steric reasons. A bulky base ends up having an easier time reaching a hydrogen on a less substituted carbon than on a more substituted carbon (transition-state stability-reactivity principle)

6. Stereochemistry: A trans-hydrogen is required.

7. Mechanism: Concerted.



Predicting E2 Eliminations:

- 1. Is the base normal or bulky?
- 2. Is the R-X 3°, 2°, or 1°?
- 3. Will E2 or $S_N 2$ occur predominantly?
- 4. Will you get Zaitsev or Hoffman elimination?
- 5. Is there a trans hydrogen available?

Draw the major Product for each of the following Reactions.



Indirect Route to Alkenes from Alkanes

Via 2 Reactions:

- 1. Bromination (reaction 1) followed by
- 2. Elimination (reaction 2)



Provide Recipe:



Synthesis of Alkenes from Alcohol (7.18)



Observations:

- 1. Zaitsev, not Hoffman elimination.
- 2. No requirement for a trans hydrogen.
- 3. Acidic conditions, need an acidic mechanism.

Mechanism (Memorize)



3 steps: Protonation – Elimination – Deprotonation

- 1. Protonation converts OH, a bad leaving group, into a very good leaving group (neutral water)
- 2. Carbocation formation is slow step (like E1 mechanism)
 - Cation stability dictates reactivity
 - Reactivity: allylic > 3° R-OH > 2° R-OH >>> 1° R-OH > vinyl, aryl
 - Allylic, 3°, and 2° work; 1°, vinyl, and aryl do not.
- 3. C-H cleavage comes last.
- 4. Mechanism typical for acid-catalyzed processes: protonate-react-deprotonate.
 - Protonation and deprotonation sandwich the key step.
- 5. Strong acidic conditions \rightarrow intermediates should be positive, not negative
- 6. Because the cation is flat, and forgets original stereochemistry, there is no trans-H requirement.
- 7. The reaction is actually reversible, an equilibrium
- 8. Get complete E1, not S_N1 , because the water that falls off in step 2 is converted to hydronium H_3O^+
- 9. Often the equilibrium is driven by distilling the alkene off as it forms (if it's low boiling due to loss of weight and being non-polar) or phase separating out from the acid layer.

Draw Products



5. Rank the reactivity of the following toward H₂SO₄-catalyzed elimination (1 most). Why?

OH OH OH

Key Issue:

Reactivity:

<u>Reaction Mechanisms (Summary and Practice)</u>

A. Recognizing/Classifying as Radical, Cationic, or Anionic: helpful for diagnosing how a mechanism might start and what kinds of intermediates are plausible

- 1. Radical
 - initiation requires both energy (either hv or Δ) and a weak, breakable heteroatomheteroatom bond
 - Cl-Cl, Br-Br, O-O (peroxide), N-Br, etc..

2 Guides for That are Usually Reliable: hv \rightarrow radical mechanism peroxides \rightarrow radical mechanism

- 2. Anionic
 - a. <u>a strong anion/base appears in the recipe</u>
 - b. no strong acids should appear in the recipe
 - c. mechanisms should involve anionic intermediates and reactants, not strongly cationic ones
 - (except for do-nothing spectators like metal cations)
 - d. The first step in the mechanism will involve the strong anion/base that appears in the recipe

3. Cationic

- a. <u>a strong acid/electrophile appears in the recipe</u>
- (Boring cations like Na⁺, K⁺, Li⁺, and Mg⁺² do nothing and do not trigger cationic
- b. no strong anion/base should appear in the recipe
- c. mechanisms should involve cationic intermediates and reactants, not strongly anionic ones
 o (except for do-nothing spectators like halide, nitrate, or hydrogen sulfate anions)
- d. The first step in the mechanism will involve the acid that appears in the recipe. The last step will often involve a deprotonation step. Often the main step occurs in between the proton-on and proton-off steps
- B. Miscellaneous Mechanism Tips
 - 1. Keep track of hydrogens on reacting carbons
 - 2. Each step in a mechanism must balance
 - 3. The types of intermediates involved (cation, anion, or radical) should be consistent with the reaction classification above
 - a. If the reaction is cationic, don't show anionic intermediates
 - b. If the reaction is anionic, don't show cationic intermediates
 - 4. Usually conditions are ionic.
 - 5. Use a reactive species, whether strong anion or an acid, to start the first step
 - a. If acidic, first step will involve protonation of the organic
 - b. If anionic, the first step will involve the anion attacking the organic.
 - 6. While it isn't always easy to figure out what is a good mechanism, you should often be able to eliminate an unreasonable mechanism.
- C. Recognizing "do-nothing anions" that do NOT trigger anionic reactions like SN2/E2
 - because the anions are highly stable and thus not very reactive/aggressive:
 - Great anion stability both explains why they are not nucleophilic and not basic

Do-nothing anions	1. Br⁻	2. Cl ⁻	3. NO ₃ -	4. HSO_4^-	5. ClO ₄ -
Conjugate Strong Acids	HBr	HCl	HNO ₃	H_2SO_4	HClO ₄

6. Classify each mechanism as radical, cationic, or anionic.



7. Which of the following mechanisms is reasonable or unreasonable for the transformation shown. <u>Identify recognition keys for things wrong with those that aren't right.</u>



Problems







Q: Which of the following mechanisms is reasonable or unreasonable for the transformation shown: H_2O, H^+

Identify recognition keys for things wrong with those that aren't right.

Problems











<u>Summary of Alkene Reactions, Ch. 8.</u> <u>Memorize Reaction, Orientation where Appropriate, Stereochemistry</u> where Appropriate, and Mechanism where Appropriate.

-all are drawn using 1-methylcyclohexene as a prototype alkene, because both orientation and stereochemistry effects are readily apparent.





Ο H 2. Me₂S

Н

°O

responsible

Note: H-bearing alkene carbon ends up as aldehyde.

• Zn common option to (CH₃)₂S in step 2

Summary of Mechanisms, Ch. 7 + 8. Alkene Synthesis and Reactions.













Ch. 8 Reactions of Alkenes

8-1,2 Introduction



- 1. Thermodynamics: Usually exothermic
 - $1 \pi + 1 \sigma \rightarrow 2 \sigma$ bonds
- 2. Kinetics: π bond is exposed and accessible

Generic Electrophilic Addition Mechanism



2 Steps: Cation formation and cation capture

- Cation formation is the slow step
 - o Cation stability will routinely determine the orientation in the first step
 - Which is preferred, $A \rightarrow B$ or $A \rightarrow C$?
- Often the cation is a normal cation **B**. Sometimes 3-membered ring cations **D** will be involved.
- In some cases, the cation will be captured by a neutral species (like water), in which case an extra deprotonation step will be involved

4 Aspects to Watch For

- 1. Orientation
 - Matters only if both of two things are true:
 - a. The alkene is unsymmetrical, and
 - b. The electrophile is unsymmetrical
- 2. Relative Stereochemistry
 - Matters only if both the first and the second alkene carbons are transformed into chiral centers
- 3. Mechanism
- 4. Relative Reactivity of Different Alkenes
 - Stability of cation formed is key

8.3 H-X Hydrogen Halide Addition: Ionic/Cationic Addition in the Absence of Peroxides



<u>Markovnikov's Rule (For Predicting Products</u>): When H-X (or any unsymmetrical species $A^{\delta+}B^{\delta-}$) adds to an unsymmetrical alkene:

• the H⁺ (or A^{δ +}) adds to the less substituted carbon (the one with more H's)

• the X⁻ (or B^{δ -}) adds to the more substituted carbon (the one with more non-H's).

• Note: Markovnikov's rule does not apply if either the alkene or the atoms that are adding are symmetrical

Examples, Predict the Products.

 $1 \qquad \qquad HBr \qquad HBr \qquad 2 \qquad HCl \qquad HCl \qquad 4 \qquad HHr \qquad HBr \qquad HBr \qquad 5 \qquad HBr \qquad HBr \qquad HBr \qquad 6 \qquad I-Cl \qquad HBr \qquad$

Does Markovnikov's Rule matter?

Mechanism



- Protonate first
- Capture cation second
- Cation formaton (step 1) is the slow step

Rank the Reactivity of the following toward HBr addition.



Issue:

Why Does Markovnikov's Rule Apply? Product/Stability Reactivity Rule.

• Formation of the most stable carbocation results in Markovnikov orientation



- This same logic applies anytime something adds to an alkene.
- You want to make the best possible intermediate in the rate-determining step.

Draw the mechanis for the following reaction:

✓ HBr

8.3B Free Radical Addition of HBr with Peroxide Initiator: Anti-Markovnikov Addition (Rxn 2)



- 1. Peroxides are radical initiators, and cause the mechanism to shift to a radical mechanism
- 2. With peroxides, the orientation is reversed to anti-Markovnikov: now the Br adds to the less substituted end and the H adds to the more substituted end of an unsymmetrical alkene
 - a. No peroxides: Br goes to more substituted end
 - b. With peroxides: Br goes to less substituted end
- 3. The anti-Markovnikov radical process works only with HBr, not HCl or HI
- 4. The radical process is faster, and wins when peroxides make it possible. In the absence of peroxides, the slower cationic process happens.

Mechanism, and Reason for AntiMarkovnikov Orientation





8.4 Addition of H-OH. Direct acid-catalyzed addition. (Reaction 3)



<u>Markovnikov</u>: $H\delta^+OH\delta^- \rightarrow H$ adds to the less substituted end of the alkene, OH adds to the more substituted end

• OH ends up on more substituted end of the alkene

Mechanism: 3 Steps.

- 1. Protonation
- 2. Cation Capture
- 3. Deprotonation



<u>Notes</u>

- 1. The sequence in which key step (cation capture in this case) is sandwiched by proton onproton off protonation-deprotonation is super common for acid-catalyzed reactions.
 - Whenever you see an acid-catalyzed process, expect to use H⁺ in first step and to deprotonate in the last step
- 2. Cation stability dictates reactivity
- 3. Cation stability explains why the Markovnikov orientation occurs. This involves the more substituted, more stable carbocation product in the rate-determining step.
- 4. The actual reaction is an equilibrium.
 - The reverse of alcohol dehydration to make alkenes!
 - A key drive is to have excess water. That pushes the equilibrium to the alcohol side.
 - Under alcohol \rightarrow alkene conditions, the equilibrium is often driven to the alkene side by having no water, or by distilling off the lower-boiling alkene as it forms.

Examples, Predict the Products.

Problems with Acid-Catalyzed Addition of Water to Alkenes

- 1. Alkenes with poor water solubility often don't add very well.
 - Can't drive the equilibrium strongly to the alcohol side in that case
 - Solvent mixtures can often help, but not always good enough
- 2. Alcohol/Alkene equilibrium sometimes poor
- 3. Carbocation rearrangements can be a problem
- 4. The degree of Markovnikov selectivity isn't always satisfactory
 - 99:1 isomer selectivity is a lot nicer than 90:10...
 - Especially if you have to purify!
- 5. Obviously you can't get the reverse, anti-Markovnikov alcohol products.

Each of these limitations, when they are a problem, can be solved by alternative recipes that indirectly add H-OH.

Draw the mechanism for the following reaction:



Does Markovnikov's Rule matter?

8.5 Indirect Markovnikov Addition of H-OH via Oxymercuration/Demercuration. Reaction4.



Notes:

- 1. Often higher yields, cleaner, faster, and easier
- 2. No restrictions
- 3. No cation rearrangements

4. Very strong, often superior Markovnikov selectivity

• OH adds to the more substituted end, H to the less substituted end

Does Markovnikov's Rule matter?

1
$$H_2O, H^+$$

1. $Hg(OAc)_2, H_2O$
2. NaBH4

$$\begin{array}{c|c} 2 \\ & & \\ \hline \\ & \\ \hline \\ 1. \ Hg(OAc)_2, H_2O \\ \hline \\ 2. \ NaBH4 \end{array}$$

H₂O/H⁺ vs Oxymercuration/Demercuration: Which should I use?

- 1. Both normally give same product
- 2. For predict-the-product problems, be able to handle either recipe
- 3. For provide-the-right-recipe problems, I will accept either answer.
 - H_2O/H^+ is easier to write!
- 4. In the real lab, the choice is decided on a case-by-case basis.
 - Default to H_2O/H^+
 - Go to oxymercuration/demercuration when direct acid-catalyzed hydration doesn't work as well as you'd like

Mechanism (For interest sake. Not for memorization, not for test.)



Notes:

- 1. "demercuration" with NaBH4 replaces the mercury with a hydrogen
- 2. The initial "oxymercuration" essentially adds $(HgOAc)^{\delta+}(OH)^{\delta-}$, and follows Markov.'s rule
- 3. The interesting new thing here is the "mercuronium" ion
- 4. This is normally drawn as a 3-ring, but can also be viewed as a resonance structure of a hybrid

Mercuronium Ion



Both participation from structures A and B are required to explain everything

- A explains why you don't get cation rearrangments, ever: you don't have a free carbocation
- A also explains structure studies, which show that the mercury is weakly bonded to the more substituted carbon
- **B** helps to explain why water adds to the more substituted carbon, which has extensive positive charge
- C doesn't contribute, isn't really involved

In the real thing, there is a long, very weak and super breakable bond between mercury and the more substituted carbon. The bond to the less substituted carbon is much shorter and stronger.



8.7 Indirect anti-Markovnikov Addition of H-OH via Hydroboration/Oxidation. Reaction 5.



Notes:

- 1. <u>Anti-Markovnikov orientation</u>: the <u>OH ends up on the less substituted end</u> of an unsymmetrical alkene; the H adds to the more substituted end
- 2. <u>Cis addition. Both the H and the OH add from the same side</u>.
- 3. When does cis/trans addition stereochemistry matter?
 - Only when both alkene carbons turn into chiral centers in the product.
 - If one does but not both, then the relative stereochemistry doesn't matter
 - For Markovnikov additions involving H-Br or H-OH, the H usually adds to a carbon that already has an H, so that in the product it is not a stereocenter.
 - In anti-Markovnikov additions, much more common for both carbons to become chiral carbons

4. Chiral products are Racemic (two enantiomers form) but not optically active

- When only one chiral center forms (often in the Markovnikov additions), any chiral product will always be racemic
- When two chiral centers form, as in the example above, of the four possible stereoisomers, you get only two of them, in racemic mixture.



Examples, Predict the Products.

Does	Does
Markov.	Stereo
Matter?	Matter?

$$\frac{1}{1}$$
 $\frac{1}{1}$ BH₃·THF

2. H₂O₂, NaOH

Does	Does
Markov.	Stereo
Matter?	Matter?



1. Which starting alkenes would produce the following products following hydroborationoxidation? Factor in the stereochemistry of the products in considering what starting materials would work.



2. Fill in recipes for converting 1-butene into the three derivatives shown.



Mechanism (For interest sake. Not for memorization, not for test.)



$$BH_3-THF \equiv H - B + O = THF'' = Tetrahydrofurn$$

Notes

- 1. Other recipes (B₂H₆, etc. are common)
- 2. BH₃-THF is a convenient complex in which the oxygen provides the extra electron pair. But the weak complex provides a small equilibrium amount of free, reactive BH₃
- 3. Free BH₃ is actually the electrophile
- 4. Because BH₃ does not have octet rule, the boron is very electrophilic
- 5. The electrophilic boron originally makes a π -complex, but then you get actual hydroboration via a 4-centered ring
- 6. The key is that both the boron and the hydrogen enter from the same side of the alkene
 - <u>concerted addition of B-H across C=C</u>
 - <u>cis addition</u>
- 7. Why do you get the orientation?
 - the B-H addition actually does follow Markovnikov's rule
 - \circ H₂B δ +H δ -
 - \circ The B is δ +, the H is δ -, because boron is a semi-metal and less electronegative than hydrogen! The only case this chapter where the hydrogen is δ rather than δ +
 - Sterics: The Boron end is pretty big, so it prefers to go to the less substituted, less hindered end of the alkene for steric as well as electronic reasons.
- 8. The NaOH/H2O2 workup is complex and beyond our scope, but replaces the B with OH with complete retention of stereochem
 - the cis stereochemistry established in the hydroboration
 - the oxygen stereo is preserved in the oxidation.

8.6 <u>Alkoxymercuration-Demercuration</u>: Markovnikov Addition of H-OR (Reaction 6)



Notes:

- 1. Everything is the <u>same as with oxymercuration-demercuration to form an alcohol</u>, <u>except you use an alcohol instead of water</u>
- 2. This results in an oxygen with it's spectator carbon chain adding rather than an OH
- 3. Strong Markovnikov orientation
 - The OR adds to the more substituted end of the alkene
 - The Hydrogen ends up on the less substituted end of the alkene
- 4. The mechanisms are analogous.

Examples, Predict the Products.

Does	Does
Mark's	Stereo?
Rule	
matter?	

1	\land	1. Hg(OAc) ₂ , CH ₃ CH ₂ OH		
		2. NaBH4		

2 OH 1. Hg(OAc)₂, 2. NaBH4

Ether Synthesis: Two Routes

- 1. From Alkene and Alcohol: By Oxymercuration/Demercuration
- 2. From R-Br and Alkoxide Anion: By $S_N 2$

Multistep Synthetic Design: Design Reactants for the Following Conversions

- 1. Note: It is often most strategic to think backward from product to precursor.
- 2. Then think back how you could access the precursor from the starting material.
- 3. There may sometimes be more than one suitable route.
- 4. There will be problems of this style/format on the next test.



8-10. H-H addition. Catalytic Hydrogenation (Reaction 7)



Notes:

- 1. Since both atoms adding are the same (H), Markovnikov orientation issues don't apply
 - You're adding a hydrogen to both the more and less substituted alkene carbon!
- 2. Stereochemistry isn't often relevant, but when it is it's cis
 - Rarely relevant because if either alkene carbon has even one hydrogen attached, addition of an additional hydrogen will result in an achiral carbon.
- 3. The reaction is substantially exothermic
- 4. But some kind of transition-metal catalyst is required to active the otherwise strong H-H bonds.

Examples, Predict the Products.

Does	Does
Mark's	Stereo?
Rule matter?	









5 H₂, Pt



8.8 X-X Dihalogen Addition: Trans Addition (Reaction 8)



Notes:

- 1. Orientation: Non-issue, since you're adding the same atom to each alkene carbon
- 2. Trans addition
- 3. Solvent matters: to get X-X addition, you need a solvent other than water or alcohol.
 - With water or alcohol, you get different products, see reaction 9

Examples, Predict the Products.

Does	Does	Chiral?
Mark.	Stereo?	
matter?		



 $6 \qquad Br_2 \qquad Br_$

Notes:

- 1. Cis and trans reactants give different products!
- 2. For any product (in this and other reactions), be able to identify whether it is chiral or not

<u>Chemical Test for Alkenes</u>: Br_2 in CCl_4 solvent is reddish/brown color. Add a few drops to an unknown organic:

- a. If the color stays reddish/brown \rightarrow the unknown does not contain any alkenes
- b. If the reddish/brown color goes away \rightarrow the unknown did have an alkene that is reacting with the bromine

Mechanism (Very important) (6.16)



Notes

- **1.** Cation Formation: Step 1
- 2. Cation capture: Step 2
- 3. Br_2 and Cl_2 are exceptionally good electrophiles
- 4. The cation that forms is a 3-membered ring
 - "Bromonium ion"
 - "Chloronium ion"
- 5. Or, it can be viewed as a π -complex, with a halogen cation sitting on a p-bond
- 6. When the nucleophile captures the cation, it must come in from the opposite face
 - Backside attack, ala S_N2
 - Trans addition results
- 7. The nucleophile actually attacks at the more substituted carbon!
 - This is contrary to S_N2 expectations!
- 8. Resonance pictures A and B help to explain things
 - a. The cyclic form A explains stereochemistry
 - If acyclic form **B** was all there was, you wouldn't need backside attack and you wouldn't get trans stereochemistry
 - b. Form **B** helps explains why the nucleophile attacks the more substituted carbon.
 - Of the two carbons, the more substituted one has the positive charge and is thus more electrophilic, in spite of steric issues.

Solvent Limitation: Solvents that are nucleophilic (water or alcohols...) successfully compete with bromide or chloride in the cation capture step.

Br₂

Draw the mechanism for:

8-9. Br-OH or Cl-OH Addition. Markovnikov Addition, Trans Addition, to form "Halohydrins" (reaction 9)



Notes:

1. Markovnikov Orientation

- OH adds to more substituted alkene carbon
- Br or Cl adds to less substituted alkene carbon
- This literally follows Markovnikov's Rule, since the relative electronegativity makes for BrOH (or ClOH) is Brδ+(OH)δ-

2. Trans addition

3. **Solvent** matters: whenever you see Br₂ or Cl₂ recipes, check whether there is a water (or alcohol) solvent

Mechanism



- 1. 3 Steps:
 - bromonium formation (cation formation)
 - cation capture/nucleophile addition
 - deprotonation (since the nucleophile was neutral)
- 2. The mechanism is closely analogous to the Br_2 or Cl_2 additions
- 3. Water is a better bromonium (chloronium) capture nucleophile than bromide (or chloride) anion
 - The large population of water molecules in the solvent give it a statistical advantage
 - When the bromide anion forms in step one, it is initially formed on the wrong side of the bromonium. It needs to swim around to the opposite side in order to attack. Usually water has already captured the cation before then.
 - Water really is inherently a better electron donor than bromide anion. This is why in water a proton goes onto water to make hydronium ion rather than going onto bromide to make covalent HBr
- 4. Notice that the water attacks the <u>more substituted</u> carbon of the bromonium (chloronium) ion

Alcohol Reactions


Examples, Predict the Products.



3
$$\bigcirc Cl_2 \rightarrow H_2O$$

5
$$\xrightarrow{\text{Br}_2}$$
 $\xrightarrow{\text{H}_2\text{O}}$

Does Does Chiral? Mark. Stereo? matter? 8-12 Epoxidation. Addition of one Oxygen (Reaction



Notes:

- 1. No orientation issues, since the same oxygen atom connects to both bonds
- 2. Cis addition: both oxygen bonds come from the same direction

Mechanism: No test Responsibility



- a. Any peracid with formula RCO₃H has an extra oxygen relative to a carboxylic acid.
- b. Any peracid can deposit the extra oxygen onto the p-bond to make the epoxide
- c. No ions are actually involved, because the leaving group is the neutral carboxylic acid

Examples, Predict the Products.











8-13 Trans OH-OH addition. Epoxidation in water. The initially formed epoxide undergoes Acid-Catalyzed Ring Opening. Reaction 11.



Does

Mark.

matter?

Does

Stereo?

Examples, Predict the Products.



$$2 \qquad \qquad \underbrace{CH_3CO_3H}_{H_2O}$$

$$3 \qquad \overline{\qquad} \qquad \xrightarrow{\text{CH}_3\text{CO}_3\text{H}} \qquad \xrightarrow{\text{H}_2\text{O}}$$

4
$$(H_3CO_3H)$$

Mech (not required)

11





- a. The nucleophile (water) attacks from the more substituted end of the protonated epoxide
 - More δ + charge there
 - The C-O bond to the more substituted end is much weaker
- b. The nucleophile adds via S_N2-like backside attack. Inversion at the top stereocenter, but not the bottom, explains the trans stereochemistry.

Chiral?

8-14 Cis OH-OH addition. Catalytic Osmylation. Reaction 12.



Does Mark.

matter?

Examples, Predict the Products.

$$1 \longrightarrow OsO_4, H_2O_2$$



3
$$\longrightarrow \xrightarrow{OsO_4, H_2O_2}$$

CH_3CO_3H
H_2O

$$4 \qquad \underbrace{\text{OsO}_4, \text{H}_2\text{O}_2}_{4}$$

$$\frac{\text{Mech: (Not required)}}{12}$$

$$12$$

$$(Not required)$$

$$12$$

$$(Not required)$$

$$(Not require$$

Chiral?

Does

Stereo?

Stereochemically complementary methods

	Skills:
$\begin{array}{ll} CH_3CO_3H/H_2O & trans \\ OsO_4/H_2O_2 & cis \end{array}$	 Given starting material and product, provide reagent Given product and reagent, what was the starting material?

1. Given starting material and product, provide reagent. Consider stereo.



2. <u>Stereochemistry Problems. Given product + reagent, what was the starting alkene?</u>



8.15-B Ozonolysis. Cleavage of Alkenes. Reaction 13



Notes

- 1. Double bond gets sliced in half, gives two corresponding carbonyls per alkene
 - So, a diene will give four carbonyls
 - A triene will give six carbonyls, etc.
 - From the product perspective, 2 carbonyls means one alkene reactant; 4 product carbonyls means two alkenes; 6 carbonyls means three alkenes, etc.
- 2. Alkene bonds and nothing else are oxidized.
- 3. Get ketones and/or aldehydes and/or formaldehyde
- 4. Zn often used in workup step two instead of dimethylsulfide

$$\frac{1}{2} \xrightarrow{1. O_3} \frac{1. O_3}{2. Me_2 S}$$

$$\begin{array}{c} 2 \\ & & \\ \hline \\ 2. \ Me_2S \end{array}$$

$$3 \qquad \overbrace{\qquad} 1. O_3 \\ 2. Me_2 S$$

4
$$\underbrace{1. O_3}_{2. Me_2S}$$

From the product perspective, 2 carbonyls means one alkene reactant; 4 product carbonyls means two alkenes; 6 carbonyls means three alkenes, etc.

1. Identify starting reactants.







2. Identify A, B, and C.



3. Design a synthetic plan for the following conversions. (Several on test)



4. What is a structure for C_3H_6 , if it reacts with Br_2 ?

Elements of Unsaturation Problems

5. What is a structure for $C_5H_{10}O_7$, if it does <u>not</u> react with H_2/Pt , but does react with H_2SO_4 to give 2 different isomeric alkenes C_5H_8 ?

6. What is a possible structure for C_5H_8 , if it reacts with H_2/Pt to give C_5H_{10} ?

7. Identify products A-C.



Polymers: Very large molecule composed of small repeating units (monomers) (8-16, ch26)

- Alkenes are common monomers for many common polymers
- Polyethylene, polypropylene, polystyrene, polyisobutylene polyvinyl chloride (PVC)
- Rubbers, plastics, piping, and all kinds of varying materials.
- Routinely named after the alkene, usually using it's common name
- Addition polymerization: chain-growth by having monomer alkenes add onto the reactive end of a growing polymer
- Reactive end is usually a cation, radical, anion, or organometallic
- Something highly unstable and highly reactive
- Initiation: Getting it started by creation of a high reactive intermediate
- Termination: Some process to depopulate the cation or radical or whatever.

Examples of Radical or Cationic Chain Growth Mechanism:



Addition Polymers

- No change in atoms, you simply add all the atoms in the reactants together to make long polymer strings.
- The repeat unit in the polymer must have the same atoms as the monomer.
- Precursors: Alkenes or Conjugated Dienes
- Polymer has one fewer double bond than monomer: monoalkene \rightarrow none; diene \rightarrow one.
- For a conjugated diene, the two middle carbons end up double-bonded in the polymer
- Initiation/recognition: Usually radical/peroxides. Sometimes acid or Lewis acid catalyzed.
- Skills: Given monomer, draw polymer
- Skills: Given polymer, recognize monomer.
- Skills: Use and understand shorthand

Ex: Mono-ene and diene polymers





Problems: Draw the monomer and the shorthand version of polymer

Draw the polymer from the following monomer, both shorthand and longstretch

CH₃ "propylene"

CO₂Me

Mixed Polymers: When two different alkenes are used.

• Some will alternate consistently, others will be kind of random



Cross-linked Polymers: When two chains are linked together

- Use some small concentration of a molecule with two alkenes and some kind of tether/spacer
- Cross-linked chains are stronger and less flexible
- The ratio of main monomer to cross-linker dictates the frequency of ties.



Polymers and Physical Properties:

Ch. 15 Conjugated Systems

Summary of Mechanisms, Ch. 15



1

2

The General Stabilization Effect of Conjugation (Section 15.1, 2, 3, 8, 9)

		Conjugated	Isolated	Notos
1	Cations			INOLES.
2	Radicals			
3	Anions			
4	Dienes			
5	Ethers	sp ² , not sp ³ !!	sp ³	An N or O next to a double bond becomes sp^2 . An isolated N or O is sp^3
6	Amines	sp ²	H Sp ³	
7	Esters	O .O. sp ²	O sp ³	
8	Amides	O sp ² N H	O H N sp ³	Very special, chapter 23, all of biochemistry, proteins, enzymes, etc.
9	Oxyanions (Carboxylates)	O O Sp ²	O Sp ³	Very special, chapter 21
10	Carbanions (Enolates)	O Sp ²	O sp ³	Very special, chapter 22
11	Aromatics			Very special, chapters 16 + 17

Conjugation: Anything that is or can be sp² hybridized is stabilized when next to π bonds.
oxygens, nitrogens, cations, radicals, and anions

Notes:

- 1. Any atom that can be sp^2 will be sp^2 when next to a double bond
- 2. "Conjugation" is when sp² centers are joined in an uninterrupted series of 3 or more, such that an uninterrupted series of π -orbitals is possible
- 3. Any sp^2 center has one p orbital

Impact of Conjugation

- 4. <u>Stability:</u> Conjugation is <u>stabilizing</u> because of π -orbital overlap (Sections 15.2, 4, 7)
 - Note: In the allyl family, <u>resonance = conjugation</u>



- 5. <u>Reactivity:</u> Conjugation-induced stability impacts <u>reactivity</u> (Sections 15.4-7)
 - If the **product** of a rate-determining step is stabilized, the reaction rate will go **faster** (product stability-reactivity principle)
 - Common when allylic cations, radicals, or carbanions are involved
 - If the <u>reactant</u> in the rate-determining step is stabilized, the reaction rate will go <u>slower</u> (reactant stability-reactivity principle)
 - Why aromatics are so much less reactive
 - Why ester, amide, and acid carbonyls are less electrophilic than aldehydes or ketones
- 6. <u>Molecular shape (Sections 15.3, 8, 9)</u>
 - The π -orbitals must be aligned in parallel for max overlap and max stability
 - The sp² centers must be coplanar

 \checkmark All four sp² carbons must be flat for the p's to align

7. <u>Bond Length:</u> Bonds that look like singles but are actually between conjugated sp² centers are <u>shorter</u> than ordinary single bonds



- 8. <u>Bond Strength:</u> Bonds that look like singles but are actually between conjugated sp² centers are <u>stronger</u> than ordinary single bonds
- 9. <u>Bond Rotation Barrier</u>: Bonds that look like singles but are actually between conjugated have much larger rotation barriers than ordinary single bonds
 - Because in the process of rotating, the π -overlap and its associated stability would be temporarily lost



- 10. <u>Hybridization</u>: Conjugated sp^2 atoms have both sp^2 and p orbitals. You should always be able to classify the hybridization of <u>lone pairs on nitrogen and oxygen</u>.
 - **Isolated** oxygens or nitrogens: sp³ atom hybridization, sp³ lone-pair hybridization, and tetrahedral, 109° bond angles
 - <u>Conjugated nitrogens</u>: sp² atom hybridization, <u>p lone-pair hybridization (needed</u> <u>for conjugation</u>), and 120° bond angles
 - <u>Conjugated oxygens</u>: sp² atom hybridization, <u>one p lone-pair hybridization</u> (needed for conjugation), <u>one sp² lone-pair</u>, and 120° bond angles



Atom Isolated vs. Conjugated Atom Hybridization Lone-Pair(s) Hybridization

Bond Angles

15.2 Diene Stability and the Stability of other Acyclic Systems with 2 Elements of Unsaturation



Stability Factors for Simple Dienes:

- 1. Isolated versus Conjugated: Conjugation stabilizes
- 2. Substitution: More highly substituted are more stable.

Stability Patterns for Regular Dienes versus Other Systems with 2 elements of unsaturation

- 3. <u>Allenes</u> = "Cumulated Dienes": <u>Less stable than dienes or alkynes</u>
 - in allenes, the central carbon is sp rather than sp² hybridized





4. <u>Alkynes</u>: <u>Less stable than dienes, but more stable than allenes</u>.

As for alkenes and dienes, more substituted alkynes are more stable less substituted alkynes

Q2: Rank the stability of the following isomers:



Q3: Rank the amount of heat produced if the isomers above were hydrogenated? Burned? 15.4 Stability of Allylic/Benzylic (Conjugated) Cations

Stability Factors for Cations:

- 1. Isolated versus Conjugated/Allylic: Conjugation stabilizes
- 2. Substitution: More highly substituted are more stable.
 - Conjugation/allylic is more important than the substitution pattern of an isolated cation (i.e. 1° allylic > 3° isolated)

Q1: Rank the stability of the following cations?



Q2: Rank the stability of the following alkene cations?



Allylic Cations, Resonance, and Allylic Symmetry/Asymmetry



- 1. Two resonance structures each (at least)
- 2. Charge is delocalized, shared
- 3. <u>Allylic cations can be symmetric or asymmetric</u>
- 4. When an allylic cation is asymmetric, it's helpful to evaluate which form would make a larger contribution to the actual hybrid
 - Cation substitution is more important than alkene substitution

Q3: For above cations, identify as symmetric or asymmetric.

7

Q4: For the following cations:

- a. identify which are allylic (would have a resonance structure).
- b. For those that are allylic, identify which are symmetric vs. asymmetric?
- c. For any asymmetric allylic cations, draw the resonance structure
- d. For any asymmetric allylic cations, identify which resonance structure would make the larger contribution to the actual resonance hybrid

b. (+)a. Ph. \oplus d. c. ⊕ e. f. Œ h. g. \oplus i. j.

Impact of Allylic Cation Resonance on Reaction Rates and on Whether One or Two Products Form (S_N1 Reactions)

- 1. <u>Rates</u>: Resonance/conjugation stability enhances rates when cation formation is ratedetermining
- 2. <u>One Product or Two?</u> Product mixtures result if an allylic cation is asymmetric.
 - two unequal resonance structures can lead to two products (structural isomers).

3. <u>Product Distribution</u>

- When two isomeric products can form, consider two things:
 - 1. Which product is more stable?
 - This will impact "product stability control" = "thermodynamic control" = "equilibrium control"
 - To assess product stability, focus on the alkene substitution
 - 2. Which resonance form of the cation would have made a larger contribution?
 - This will often favor "kinetic control", in which a product which may not ultimately be the most stable forms preferentially
- 4. **Position of Cation Formation**: When a conjugated diene is protonated, consider which site of protonation would give the best allylic cation.

<u>Q1</u>: Key: Think about the cation! For the bromides A-C:

- a. Draw the cation intermediates.
- b. If an allylic cation is involved, recognize as symmetric or asymmetric.
- c. Rank the reactivity of the three bromides.
- d. Draw the product or products. Be clear to notice whether you'd get one isomer or two.
- e. If two products are possible, identify which is more stable (the "thermodynamic product") based on product alkene stability.
- f. For the asymmetric allylic cation, identify which resonance structure makes a larger contribution to the resonance hybrid. Does this lead to the "thermodynamic" (more stable) product, or to the "kinetic" (less stable) product?

$$H_2O(S_N1)$$

$$H_2O(S_N1)$$

$$H_2O(S_N1)$$

$$H_2O(S_N1)$$

Br

С

Impact of Allylic Cation Resonance on Addition of H-X to Conjugated Dienes.

• Notes on predicting products when H-X adds to a diene.

Questions/Issues to Deal With When Predicting Product(s).

- 1. Always protonate first on an outside rather than inside carbon.
- This will give an allylic rather than isolated cation
- 2. Is the diene symmetric or asymmetric?
 - If it's symmetric, it doesn't matter which outside carbon you add to first.
 - If it's asymmetric, then protonating at different ends will likely give allylic cations of unequal stability. Thus you should decide which protonation site will give the best allylic cation.
- 3. Is the allylic cation (once you have protonated) symmetric or asymmetric?
 - If it's symmetric, you'll get one structural isomer.
 - Is it's asymmetric, you'll get two structural isomers.

Question 2: Key: Think about the cation! For the dienes A-C,

- a. Draw the cation intermediates.
- b. If an allylic cation is involved, recognize as symmetric or asymmetric.
- c. Rank the reactivity of the three bromides.
- d. Draw the product or products. Be clear to notice whether you'd get one isomer or two.
- e. If two products are possible, identify which is more stable (the "thermodynamic product") based on product alkene stability.
- f. For the asymmetric allylic cation, identify which resonance structure makes a larger contribution to the resonance hybrid. Does this lead to the "thermodynamic" (more stable) product, or to the "kinetic" (less stable) product?
- g. When two products form, classify each as a "1,2" or "1,4" product



<u>Sections 15.5,6</u> 1,2 vs. 1,4 Addition to Conjugated Dienes: "Kinetic" vs. "Thermodynamic" Control

- 1. "Thermodynamic Control" = "Product-Stability Control" = "Equilibrium Control"
 - This is when <u>the most stable</u> of two possible <u>products</u> predominates.
 - Use Alkene Stability to identify which product is more stable.
 - The most stable product will be preferred if either:
 - The two products can equilibrate, or
 - The more stable product involves a more stable transition state
- 2. Kinetic Control: If the less stable of two possible products predominates.
 - This will always require that for some reason the less stable product forms via a better transition state (transition-state stability/reactivity principle). Common reasons:
 - Charge distribution in an allylic cation or radical.
 - Proximity of reactants. In an H-X addition to a diene, often the halide anion is closer to the "2" carbon than to the "4" carbon of the allylic cation.
 - Steric factors. (Why bulky E2 base give less stable Hoffman alkenes.)
- 3. <u>**Temperature Factor**</u>: When allylic halides are produced, the "thermodynamic" product increases at higher temperature due to equilibration.

Example:



Mech (and why)

What about the following? Do they form, and if not why not?



More H-X to Conjugated Dienes Practice

- 1. Draw the mechanism, including both resonance structures for the best allylic cation.
- 2. Predict the products for the following reaction.
- 3. Identify each product as 1,2 or 1,4 product.
- 4. Identify which product is the "thermodynamic" product, and which might be the "kinetic".
- 5. One product X is the major product at low temp, but the other product Y is major at higher temperatures. Assign "X" and "Y" to the appropriate products.

1.0 D-Br

Review on predicting products when H-X adds to a diene.

- 1. Always protonate first on an outside rather than inside carbon.
 - This will give an allylic rather than isolated cation
- 2. Is the diene symmetric or asymmetric?
 - If it's symmetric, it doesn't matter which outside carbon you add to first.
 - If it's asymmetric, then protonating at different ends will likely give allylic cations of unequal stability. Thus you should decide which protonation site will give the best allylic cation.
- 3. Is the allylic cation (once you have protonated) symmetric or asymmetric?
 - If it's symmetric, you'll get one structural isomer.
 - Is it's asymmetric, you'll get two structural isomers.

Mixtures of 1,2 and 1,4 addition also occur when dihalogens (Br2, Cl2) add to dienes

Q2: Draw the major products when the diene above reacts with Br_2 . Which would you expect to be the "thermodynamic" product?

15.7 Allylic/Benzylic Radicals and Allylic Halogenation

Stability Factors for Radicals:

- 1. Isolated versus Conjugated/Allylic: Conjugation stabilizes
- 2. Substitution: More highly substituted are more stable.
 - Conjugation/allylic is more important than the substitution pattern

Impact of Radical Resonance on Reactivity and Product Formation: Allylic Radical Bromination is Fast!

- 1. **<u>Rates</u>**: Allylic bromination is fast.
- 2. Position of Radical Formation: Allylic positions react.
- 3. <u>Product Distribution A:</u> Unequal allylic positions can each lead to products.
- 4. **<u>Product Distribution B:</u>** Asymmetric allylic radicals product two bromide isomer.

Review on predicting products in allylic radical brominations.

- 1. Is the alkene symmetric or asymmetric?
 - If it's symmetric, it doesn't matter which allylic carbon you convert to a radical.
 - If it's asymmetric, then you can remove a hydrogen from different allylic sites and make different allylic radicals, each of which can lead to products.
- 2. For each allylic radical, is it symmetric or asymmetric?
 - If it's symmetric, it will lead to one structural isomer bromide.
 - Is it's asymmetric, it will lead to two structural isomer bromides.



"<u>NBS</u>" = <u>N-Bromos</u>uccinimide = More commonly used than Br₂/hv for allylic/benzylic radical brominations. Maintains dilute [Br₂], absorbs HBr. Prevents Br₂ or HBr from undergoing ionic addition to alkenes. More convenient to weigh out (solid). Some mechanistic complexity. Often higher yields.

Practice Problems

- a. Draw the radical intermediates, including resonance structures
- b. Ranks the reactivity of A, B, and C.
- c. Draw the product or products for the following reactions



Allylic Anions

- 1. Allylic anions are stabilized, just as are cations and radicals
- 2. Anion stability impacts acidity
 - when something neutral functions as an acid, it releases H^+ and produces an anion

Question 1: Compare the acidity of cyclpentene to cyclopentane. One is a quintillion times more acidic than the other. Which is it, and why?

Question 2: Compare the acidity of acetone, 2-methylpropene, and 2-methylpropane



Section 15.10 Allylic Halides and S_N2 Reactions. Allylic Systems Are Really Fast!



<u>Test responsibility</u>: You'll want to recognize allylic halides as being really $S_N 2$ fast for ranking problems.

Not for Test Responsibility, but For Your Interest:

Q: Why does conjugation make allylic halides so fast for $S_N 2$ reactions, when there doesn't seem to be any conjugation in either the starting material or the product?

A: Because the backside-attack transition-state is stabilized by conjugation! (Transition state-stability-reactivity principle).



- 1. Neither the product nor the reactant has conjugation, so it's hard to see why conjugation should apply
- 2. However, in the 5-coordinate T-state the reactive carbon is sp² hybridized
 - the nucleophile and the electrophile are essentially on opposite ends of a temporary porbital.
- 3. That transient sp² hybridization in the transition-state is stabilized by π -overlap with the adjacent p-bond.
- 4. This stabilization of the transition-state lowers the activation barrier and greatly accelerates reaction

<u>Section 15.11</u> The Diels-Alder Reaction. The Reaction of Conjugated Dienes (Dienes) with Electron-Poor Alkenes (Dienophiles) to make Cyclohexenes.

Quick Overview Summary



A. The General Diels-Alder Reaction



- 1. Electronics: The diene HOMO reacts with the dienophile LUMO
 - Effectively the diene is the nucleophile and the dienophile functions as the electrophile
- 2. The <u>dienophile</u> usually <u>needs an electron-withdrawing attachment</u> ("W") (at least one)
 - This makes the dienophile more electrophilic
 - Electron Withdrawing Groups to Memorize:



- Keys:
 - The atom that is connected to the alkene has δ + charge
 - Anything with a double-bond to a heteroatom tends to have this

Q1/example: Rank the reactivity of the following alkenes as dienophiles. The actual relative reactivity ratios are 50,000 : 1,000 : 1. Huge differences.





Q2: Rank the reactivity of the following dienophiles:





- 3. Energetics:
 - **Bonds broken**: 3π bonds
 - **Bonds made**: 2σ bonds, 1π bond
 - Enthalpy: The net replacement of 2π bonds (weaker) with 2σ bonds is normally strongly enthalpy favored
 - Entropy: The high required organization of the concerted transition state makes the reaction entropy disfavored.
 - Heat normally required to overcome entropy

4. Simple Mechanism (Good enough for test)



All bond making and breaking happens at once: *3 π -bonds break *2 σ -bonds and 1 π -bond form

The diene is really the "nucleophile" (HOMO) The dienophile is really the "electrophile" (LUMO

5. Orbital Picture



- a. the p orbitals on the dienophile overlap with the p-orbitals on C1 and C4 of the diene
- b. the overlapped p orbitals from the diene and dienophile end up being σ bonds in product
- c. the leftover p orbitals on C2 and C3 end up overlapping to give the π bond in product
- d. the diene must be in the s-cis conformation; in the zigzag s-trans layout, can't react
- e. Not tested: perfect HOMO/LUMO orbital symmetry match (Section 15.12)

B. Predicting Products When the Diene or the Dienophile (or both) is Symmetric

- 1. Always make a cyclohexene 6-ring product
- 2. Number the diene from 1-4, and identify those four carbons in the product ring.
- 3. A double bond in the product will always exist between carbons 2 and 3.
- 4. Any substituents on the diene or dienophile are spectators: they will be attached to the same carbons at the end.
- Beware of cyclic dienes
- Beware of dienes that are drawn in their zigzag s-trans form, but could react following rotation into an s-cis form

Noteworthy







5

6



C. Stereochemistry: For Cis- or Trans- Disubstituted Dienophiles

- Both carbons of a disubstituted dienophile usually turn into stereocenters.
- 1. Cis in \rightarrow cis out: If two substituents on the <u>dienophile</u> are cis to begin with, they will still have a cis relationship on the product cyclohexene
- 2. Trans in → trans out: If two substituents on the <u>dienophile</u> are cis to begin with, they will still have a cis relationship on the product cyclohexene
- Note: this is for the <u>dienophile only</u>. The diene alkenes may also have substitution such that one or both diene double bonds are cis or trans, but the "cis-in-cis-out" guideline does not apply to the diene.



• <u>Why</u>: Because of the concerted mechanism. The diene is basically doing a concerted "cis" addition to the dienophile. The attachments on the dienophile never have opportunity to change their position relative to each other.

2 +
$$O_2N$$
 NO₂ heat

3
$$+ \bigcirc CO_2CH_3 \\ + \bigcirc CO_2CH_3 \xrightarrow{\text{heat}}$$



D. Structural Factors for **Dienes**

1. <u>s-cis (cisoid) diene conformational requirement</u>: The diene must be locked "s-cis" or be able to single-bond rotate it's way into the "s-cis" (cisoid) conformation in order to react







- Normally the s-cis conformation is less stable than the s-trans conformation (sterics).
- Only the minor fraction of a diene in the s-cis conformation is able to react
- The larger the equilibrium population in the s-cis conformation, the greater the reactivity
- 2. For an acyclic diene, a "Z" substituent on either (or both) of the diene alkenes causes major steric problems for the s-cis conformation, reduces the equilibrium population of s-cis diene, and thus reduces Diels-Alder reactivity

Q1: For the dienes A-Z, circle the letters for those that are in a reactive s-cis conformation.

Q2: For the acyclic dienes C-Z, identify any double bonds the are E or Z.

Q3: Match acyclic dienez C-Z with the alternate s-cis/s-trans form shown below.

Q4: For the dienes **A-E**, try to rank their probable Diels-Alder reactivity based on the probable relative population of their s-cis conformations. (or match: 100%, 3%, 001%, 0.000001%, 0%)

Q5: Try to redraw **D** and **E** into their s-cis forms



1

Ch. 16 Aromatic Compounds



Facts to Accommodate

- 1. 4 elements of unsaturation
- 2. All C-C bonds are same length, not alternating (contrary to expectation based on structure **A**)
- 3. Only 1 isomer of 1,2-dibromobenzene (contrary to expectation based on structure A)
- 4. Unlike alkenes, does not undergo addition reactions (contrary to expectations based on A)
- 5. Extreme stability indicated by combustion or hydrogenation tests

\sim	H_2/Pt	Br ₂	HBr	BH ₃	Hg(OAc) 2/H2O	Etc.
D	Reacts	Reacts	Reacts	Reacts	Reacts	
A	No Reaction	No Reaction	No Reaction	No Reaction	No Reaction	

Hydrogenation: Measurement Tests for the Extraordinary Stability of Benzene



- Hydrogenation is normally very exothermic, but not for benzene
- The less favorable hydrogenation reflects greater stability
- The stability difference is over 30 kcal/mol: huge
 - Butadiene gains <4 kcal/mol of stability from it's conjugation

16.3,4 Benzene Molecular, Structural Details, and Molecular Orbitals

1. Some unrerent pictures of benzene				
	H H H H H			
<u>a) Simplest</u>	Illustrates:	a) Easy to see π-	<u>a) Easy to see the π-</u>	
<u>b) Ideal for</u>	a) delocalization of	system	system, undistracted	
<u>mechanisms</u> , helps	b) equivalence of	b) Helps explain why	by the hydrogens	
keep track of the	bonds	the C-C bonds are all	_	
electrons	d)complete planarity	the same		

1. Some different pictures of benzene

2. Notes on Pictures and Structural Features

- 1. All 6 carbons are sp^2 , with one p orbital each
- 2. 120° angles, so all 6 carbons and each of their attached hydrogens are all co-planar.
- 3. Perfectly flat.
- 4. Perfect 120° angles, no angle strain whatsoever
- 5. Complete symmetry
- 6. Each C-C bond is equal in length and strength
- 7. Each C-C bond is longer than a normal double but shorter than a normal single bond

- "1.5" bonds, as we see from resonance.
- 8. 6π -electrons are delocalized throughout the ring.
 - Complete racetrack
- 9. Resonance delocalization, stabilization
- 10. Note: not all " π racetracks" are stabilized



No extra stability Actually somewhat destabilized

3. Molecular Orbital for Benzene (11.5)



- All and only the bonding molecular orbitals are completely filled. Special stability
- But how can you know what the molecular orbitals will look like for other rings?

<u>Molecular Orbital Rules for any cyclic π -system (in which every atom in the ring is sp²-hybridized and has an overlapping p-orbital):</u>

- 1. If all and only the bonding molecular orbitals are occupied \rightarrow good ("aromatic")
 - Aromatic means highly stabilized
- 2. If any nonbonding or antibonding MO's are occupied, or if any bonding MO's are not completely occupied → bad, poor stability ("antiaromatic")
- 3. Notes:
 - Any orbital below nonbonding line \rightarrow bonding orbital
 - Above nonbonding line \rightarrow antibonding
 - On nonbonding line \rightarrow nonbonding

(Note: This page will NOT be tested. This is for your interest only. But definitely note the notes on the bottom! They will help explain what follows.)

Frost Diagram/Polygon Rule: (11.19) For a complete ring of sp² centers,

- 1. Draw the ring/polygon with a vertex down, basically inside what would be a circle
- 2. Each apex represents a molecular orbital
- 3. A horizontal line through the middle of the ring provides the non-bonding reference point
- 4. Populate the MO's as needed depending on how many π -electrons are available

Practice Problem

- 1. Draw the MO's for 3-, 4-, 5-, and 6-membered cyclic π systems.
- 2. Fill in the orbitals and circle the following as good=stable=aromatic or not.



NOTES:

- In practice, any 5-, 6-, 7-, and 8-membered rings with a complete complete ring of sp² centers **ends up with three bonding molecular orbitals**.
- With three bonding orbitals each, in each case it will take 6 π -electrons to completely fill the bonding orbitals.
- Since completely filling the bonding orbital \rightarrow aromaticity, six π -electrons is the magic number for these rings sizes to be aromatic

3

NOTES:

- In practice, any 5-, 6-, 7-, and 8-membered rings with a complete complete ring of sp² centers **ends up with three bonding molecular orbitals**.
- With three bonding orbitals each, in each case it will take 6 π -electrons to completely fill the bonding orbitals.

Since completely filling the bonding orbital \rightarrow aromaticity, six π -electrons is the magic number for these rings sizes to be aromatic

(11.19) Huckel's Rule: Aromatic vs Antiaromatic vs Nonaromatic.

A practical guide to recognize:

- Aromatic (highly stabilized) versus
- anti-aromatic (highly destabilized) versus
- **non-aromatic** rings (no special great stability or instability).

<u>Huckel's Rule</u>: For a **planar**, **<u>continuous ring</u>** of π -**orbitals**, (sp² all around):

- If the number of π -electrons = 2,6,10 etc. (4N + 2) \rightarrow AROMATIC, STABILIZED
- If the number of π -electrons = 4,8,12 etc. (4N) \rightarrow Anti-aromatic, destabilized
- Why: the 4N+2 rule always goes with favorable Frost diagrams and favorable orbital populations: bonding and only bonding MO's are always filled.

Generality: Huckel's Rule applies for

- 1. Cycles (one-ring)
- 2. Bicycles or Polycycles (2 or more rings)
- 3. Ionic compounds, and
- 4. Heterocycles (rings containing Oxygen or Nitrogen).

Practice application on following page.
<u>Practice Problems: Classify each of the following as Aromatic (circle them) or not. For those that aren't, are there any that are Antiaromatic? (square them)</u>

Keys:

- 1. Do you have an uninterrupted sp² ring?
- 2. Apply Huckel's Rule: Do you have 2,6,10 etc. π electrons?
- 3. Applying Huckel's Rule requires that you can accurately count your π -electrons. Be able to count:
 - Anions: contribute 2π -electrons
 - Cations: contribute 0π -electrons
 - Heteroatoms (O or N): can provide 2 π -electrons if it helps result in aromatic stability.

Note: For those that are not aromatic, why not?

1. Lacks cyclic sp² ring 2. Lacks Huckel's rule electron count

3. \triangle \triangle 2. 1. 🛆 4 5 6. 7. 8. 9. 10. 11. 12. CI 13. 14. 15. 16. 18. 19. 17. 20. 21. 22. 23. 24 NН 25 L 26 28 27.

16.8 Aromatic Ions

3 common, important Aromatic Ions



Problem 1: The following substrates have widely differing reactivity toward H₂O solvolyis. (The fastest is more than a million times faster than 2nd fastest, and the slowest more than a hundred times slower than the second slowest). Rank the reactivity. (Key: What kind of reaction would happen, and what determines reactivity?)



Problem 2: The following have enormous differences in <u>acidity</u>. (10⁻²⁰, 10⁻⁴², 10⁻⁵⁰, 10⁻⁵⁶) Key:





Nitrogens: Atom hybridization, Lone-Pair hybridization, and Basicity

- Amine nitrogens are normally basic, but not when the N-lone pair is p-hybridized
- Rule: If a nitrogen lone pair is p (used in conjugation) \rightarrow nonbasic
- Nitrogen lone-pair basicity: sp³ > sp² >>> p

Situations	<u>N-Atom</u>	N-Lone Pair	N-Basicity
1. Isolated	sp ³	sp ³	Normal
2. Double Bonded	sp^2	sp^2	Normal (a little
			much)
3. Conjugated (not itself double	sp ²	р	Nonbasic
bonded, but next to a double bond)			

Why are p-lone pairs so much less basic?

• Because conjugation/aromatic stability in the reactant is lost upon protonation.

$$\begin{array}{c}
\hline \\ NH + H^{\oplus} \implies & \swarrow^{\oplus} \\
 aromatic, \\
 stabilized \\
\end{array}$$
nonaromatic,
nonstabilized

Problem: For each nitrogen, classify:

- a) hybridization of the Nitrogen atom
- b) hybridization of the Nitrogen lone-pair
- c) basicity of the Nitrogen (basic or nonbasic)







16.10 Polycyclic Aromatics (needn't memorize names). Not for testing, For Your Interest.



16.13 AROMATIC NOMENCLATURE

- 1. <u>Memorize</u> Special Names.
- Six Special Monosubstituted Names You Must Memorize



Three Special Heterocyclic Common Names You Must <u>Memorize</u>

Pyridine

N-hybridization: sp² N-lone-pair: sp² N-basicity: reasonably normal

The lone pair is not used in the π -system; the sp² points in plane of paper, and has normal basicity.





Pyrrole

N-hybridization: sp² N-lone-pair: p N-basicity: Nonbasic

The lone pair is used in the π -system and is counted toward the 6 electrons for Huckel's rule. Because the lone pair is p, pyrrole is nonbasic.

<u>Furan</u>

O-hybridization: sp² O-lone-pairs: one p, one sp²

The p lone pair is used in the π -system and is needed to get the 6 electrons needed for Huckel's rule. But the sp² lone pair is in the plane of the ring, extending straight out.



2. Mono-substituted benzenes, if not one of the special memory names: use "benzene" as core name





- 3. Di- or polysubstituted aromatics
 - a. If one of the "special" memory names can be used, use that as the core name and number with the special substituent on carbon 1.
 - b. Special Terms:
 - "ortho" or o-
 - "meta" or m-
 - "para" or p-
- 1,2 relationship 1,3 relationship
- 1,4 relationship



. С



8

- 4. As a substituent, benzene is named "phenyl"
 - "phenyl" = $C_{6}H_{5}$ = a benzene group attached to something else, named as a substituent



• Three Shorthands for phenyl



PhBr

C₆H₅Br



• Not for testing, but to explain why the word "phenyl" instead of "benzyl" is used for the C6H5 group: It's because "benzyl" means some else, "Benzyl" = PhCH2



9

This Page is NOT for TESTING, just For Your Interest if time permits. Some Complex Aromatics in Nature

1. Amino Acids. 3 of 22 amino acids found in human proteins are aromatic



"Essential"-have to eat them, since body can't make the benzene rings

2. Nitrogen Bases: Purine, Pyrimidine, Imidazole.

Nitrogen Bases Purine, Pyrimidine, Imidazole. Substituted derivatives of purine and pyrimidine are the stuff of DNA and RNA. The basicity of their nitrogens is crucial to genetics, replication, enzymes, and protein synthesis.



3. Nitrogen Bases: Purine, Pyrimidine, Imidazole. Nicotinamide Adenine Dinucleotide (NAD+) and NADH. Important Redox reagents.



4. Polychlorinated Biphenyls (PCB's). High stability as insulators, flame-retardants make them so stable that they are hard to get rid of!



Ortho/Para Activating/ Or Meta Deactivating Directing Book Br + Br₂ FeBr₃ (cat.) Deactivating **Ortho/Para** 17.2 (+ HBr) 1 (or Fe cat) CI Deactivating **Ortho/Para** 17.2 + Cl₂ AlCl₃ (cat.) (+ HCI) The halides are unique in being deactivating but ortho/para directing. All other o/pdirectors are activating, and all other deactivating groups are m-directors. Mech required NO₂ Н (+ H₂O) + HNO₃ $\xrightarrow{\text{H}_2\text{SO}_4}$ (i Deactivating Meta 17.3 2 The product can be reduced to Ar-NH₂ by Fe/HCl or Sn/HCl. Nitration/Reduction provides an effective way to introduce an NH₂ group. Reduction converts m-directing NO₂ group into an o/p-directing NH₂ group. Mech required. Ortho/para 17.10 Activating H AICI₃ (cat.) (+ HCI) 3 a. Restricted to 3°, 2°, or ethyl halides. 1° halides suffer carbocation rearrangements. b. Since product is more active than starting material, polyalkylation is often a serious problem.

5 Major Electrophilic Aromatic Substitution Reactions

	c. Fails with strongly deactivated benzenes.	Mech 1	<u>required.</u>	
4	H = H = H = H = H = H = H = H = H = H =	Deactivating	Meta	17.11
	 a. The product can be reduced to -CH₂R by Zn(Hg)/H0 b. The acylation-reduction sequence provides an effect group. c. Reduction converts meta-directing acyl group into a group. 	Cl. tive way to introd n ortho/para-dire <u>Mech require</u>	luce a 1° alkyl cting alkyl <u>d.</u>	
5	$H + SO_3 \xrightarrow{H_2SO_4} SO_3H$	Deactivating	Meta	17.4
	The sulfonyl group is a useful para-blocking group, sin treatment with H_2O/H^+ .	ice it can later be No mech requi	removed upon red.	

5 Major Aromatic Support Reactions

		Activating <u>/</u> Deactivating	Ortho/Para Or Meta <u>Directing</u>	<u>Book</u>
6	NO ₂ Fe, HCl or Sn, HCl	19.21	Ortho/Para	19.21
	 Reduction converts meta-director into an ortho- Fe, Sn, or several other reducing metals can work 	para director. rk.		
7	$ \begin{array}{c} O \\ H \\ HCI \end{array} \xrightarrow{H \\ HCI} H \\ HCI \\$	17.12	Ortho/Para	17.12
	 Clemmensen reduction converts meta-director i Acylation (#4) followed by Clemmensen Reduction method for introducing a 1° alkyl group. (Direction halide, reaction #3, fails due to cation rearrange) 	nto ortho-para di etion (#7) is the s et alkylation with ment problems	rector. tandard a 1° alkyl .)	
8	H_2O, H^+	17.4		17.4
	 The sulfonyl group is a useful and reversible pa be temporarily put on (reaction 5) but then treatment with H₂O/H⁺ (reaction 8). The sulfonation/other reaction/desulfonation ortho-substitution of an o/p director. 	ara-blocking grou can be remov sequence is cru	up, since it can ed later upon cial for clean	
9	$CH_3 \xrightarrow{\text{CH}_3} \frac{1. \text{ KMnO}_4, \text{ NaOH}}{2. \text{ H}_3\text{O}^+} CO_2\text{H}$	17.14	Meta	17.14
	 Oxidation converts ortho/para-director into a me Side alkyl chains longer than methyl can also be the same way, although more time and heat is re For test purposes, just writing KMnO₄ will be C requires a basic solution for the KMnO₄ to work actually required to isolate the neutral carboxyli 	eta-director. e oxidized to ben equired. DK. But the real x, so an acidic wo c acid.	zoic acid in reaction orkup step is	
10	H H Br ₂ , hv or H Br peroxides or NBS	17.14		17.14
	 Bromination occurs via free-radical mechanism It is selective for substitution at the benzylic radical intermediate is resonance-stabilized. Note: keep distinct Br₂/FeBr₃ from Br₂/peroxid Product is subject to S_N2 substitutions (benzylic and E2 eliminations with bulky bases. "NBS" is N-bromosuccinimide, which functio avoids competing reactions caused by Br₂ and F 	position becaus es! bromides are es ns just like Br ₂ / IBr.	e the benzylic specially good) peroxides, but	

<u>Summary of Mechanisms, Ch. 17</u> <u>Electrophilic Aromatic Substitutions</u>





Section 17.1 Electrophilic Aromatic Substitution



- 1. The addition step, generating the carbocation, is the rate-determining step
- 2. Any extra <u>substituents that stabilize the carbocation will make the reaction faster</u> (the product stability-reactivity principle). And vice-versa...
 - <u>Electron-donating groups</u> will stabilize carbocations and accelerate (<u>activate</u>)
 - <u>Electron-withdrawing groups</u> that destabilize carbocations will decelerate (<u>deactivate</u>)
- 3. As shown below, the **<u>positive charge is shared by resonance</u>** over three carbons: the carbons that are **<u>ortho and para</u>** relative to the carbon where the electrophile actually adds
 - Positive charge does not appear at either of the positions meta to where the electrophile adds
- 4. If a substituent is ortho or para relative to the carbon where the electrophile actually adds, the substituent will be next to a positive charge in one of the three resonance structure, and will have a large electronic effect, for good (donors) or bad (withdrawers)
 - If a substituent is an electron donor (cation stabilizer), it will be very beneficial if the electrophile adds ortho or para relative to the substituent. Therefore ortho or para addition will be much faster than meta addition.
 - > Thus electron donors (cation stabilizers) function as ortho/para directors.
 - If a substituent is an electron withdrawer (cation destabilizer), it will be very harmful if the electrophile adds ortho or para relative to the substituent. Therefore ortho or para addition will be much slower than meta addition.

Thus electron withdrawers (cation destabilizers) function as meta directors.

• Note: meta directors are meta directors not because meta addition is especially good; rather, it's because meta isn't nearly as bad as ortho or para addition, so meta addition is the best option available. But keep in mind that it still is slower than normal.

Three Resonance Structures for Every Electrophilic Aromatic Substitution



- A substituent that's good for one of these cation forms (donor) is good for the addition:
 - This results in activation (kinetics)
 - and ortho/para addition (orientation)
- A substituent that's bad for one of these cation forms (withdrawer) is bad for the addition:
 - This results in deactivation (kinetics)
 - And meta addition (orientation)

Formation of the Active Electrophiles

- 1. In each case, the cationic form of the thing that adds must be generated
- 2. The arrow pushing in the E+ generation always involves an arrow going from the cation precursor to the Lewis or Bronsted acid
- 3. For class, we will focus on sulfuric acid as Bronsted acid, and AlCl₃ or FeBr₃ as Lewis acids
 - But in an actual synthesis lab, other Bronsted or Lewis acids are available and may sometimes provide superior performance.



<u>Note</u>: The <u>acids</u> really need be used in only <u>catalytic</u> quantities. The active acids are regenerated during the deprotonation step.



Additions to Substituted Benzenes. The Effect of Substituents on Reactivity Rates and the Position of Substitution. (17.4, 5, 6)

Three Issues

- 1. Activators versus Deactivators
- 2. Electron Donors versus Electron Withdrawing Groups
- 3. Ortho-Para directors versus Meta Directors

Fact: The rate determining step is the cation addition step

- The transition state much resembles the carbocationic product of that step
- What's good for the cation is good for the reaction rate (product stability-reactivity principle)

Cation stabilizers = <u>electron donors</u> \rightarrow good for cations \rightarrow good for rates = <u>activators</u> Cation destabilizers = <u>electron withdrawers</u> \rightarrow bad for cations \rightarrow bad for rates = <u>deactivators</u>

<u>Problem</u>: Rank the reactivity towards HNO_3/H_2SO_4 (The fastest is 25 times faster than the middle, the slowest one is less than $1/100^{\text{th}}$ as fast as the middle.)



Position of Substitution: When an electrophile adds to a substituted benzene, does it add **Ortho, Meta, or Para to the pre-existing substituent?** Ortho-para directors versus Meta Directors

• When an electrophile adds to a substituted benzene, it can potentially come in at three different positions: ortho, meta, or para





The Situation with an Electron **Donor**/Cation Stabilizer (Ortho-Para Director) (Section 17-6)



Summary: Electronic Factor: An electron donor (cation stabilizer) is especially beneficial electronically when the electrophile adds ortho or para relative to the donor.

Thus donors are ortho/para directors.

Steric Factor: Ortho addition relative to the donor is always destabilized somewhat by steric interactions. Thus, when addition para relative to the donor does not involve any steric interactions, (usually but not always the case), para addition is faster than ortho addition.

The Situation with an Electron Withdrawer/Cation Stabilizer (Ortho-Para Director) (12.13)



Summary: An electron withdrawer (cation destabilizer) is especially harmful electronically when the electrophile adds ortho or para relative to the withdrawer. Thus withdrawers are meta directors. Not because meta is that good; it's just not as bad as ortho or para.

Note: Meta is still deactivated somewhat, it's just not as slow as ortho or para addition.

Halogenation Reactions (17-2)

- Note: In the presence of Br₂, Fe metal is converted directly into FeBr₃, so sometimes Fe rather than FeBr₃ is used
- Many other Lewis acids can accomplish the same reactions

Draw the products for the following reactions.

$$1 \qquad \qquad H_3C \qquad + Br_2 \xrightarrow{\text{FeBr}_3 (\text{cat.})}$$

2
$$+ Cl_2 \xrightarrow{\text{AlCl}_3 (\text{cat.})}$$

- 3 Draw the mechanism for the first reaction above.
 - Identify the slow step.
 - Draw in all three resonance structures for the cation.
 - Circle the best resonance structure.

<u>Tips:</u>

- Always draw the hydrogen on the reacting carbon
- For resonance structures, keep substituent, key H, and adding group in each picture
- Never draw the + charge on the tetrahedral center
- At the cation stage, make sure you never draw a double bond to the tetrahedral center (that would make 5 bonds!)



Seeing the Mechanism and Resonance Structures from Different Perspectives

NOTES:

- 1. These focus on drawing the resonance structures and seeing how the positive charge is delocalized in the cation.
- 2. Notice that regardless of which position the electrophile adds to, the positive charge still ends up delocalized onto the positions ortho and para <u>relative to the site of addition</u>
- 3. Notice that the site of addition does <u>not</u> have positive charge
- 4. Notice that the hydrogen that is lost is from the same carbon where the electrophile adds, not from an ortho carbon

4 Classes of Substituents: Memorize! (Sections 17-6-8)

Donating?	Memorize the list	Activating/Deactivating	Directing Effect
	OH, OR, NH ₂ , NHR, NR ₂	Strong Activators	Ortho/para directors
	R, Ar	Weak Activators	Ortho/para directors
	Cl, Br	Weak Deactivators	Ortho/para directors
	Carbonyl, NO ₂ , CN, SO ₃ H	Strong Deactivators	Meta directors

<u>Note</u>: <u>Halogens are a special case</u> that are ortho-para directors despite being deactivating Otherwise, the following pattern is general:

- Activator = ortho-para director (and vice versa, with exception of halides)
- Meta director = deactivator (and vice versa, with exception of halides)

Special Resonance/Conjugation with Oxygen and Nitrogen Substituents



Section 7-8. Halogens. Special Case: Weak Deactivators, but still ortho-para directors.

<u>Explanation (not for test)</u>: Halogens are both withdrawers (based on their electronegativity) but also donors (through resonance/conjugation/ π -donation)

- Withdrawers, because of the polarized, electronegative C-X bond
- Donors via the π-conjugation
- The withdrawing effect is stronger, thus they are overall deactivators, whether ortho, meta, or para
- The π-conjugation only benefits with ortho-para addition
- Because of the conjugation/resonance factor, ortho-para addition isn't as destabilized as meta addition.





Electronegativity withdrawer (through sigma bond) σ-Withdrawer Conjugation/resonance donor Through lone-pair π -system π -Donor

Rank the reactivity of the following towards Br2/FeBr3.



Shown are 9 different sites for possible addition. Rank all 9, from most to least reactive.



Nitration Reaction (17-3)

2	$H \rightarrow HNO_{3} \rightarrow H_{2}SO_{4} \rightarrow (+H_{2}O)$	Deactivating	Meta	17.3
6	$ \begin{array}{c} $	Activating	Ortho/Para	19.21

Draw the major product.

$$CI \longrightarrow HNO_3 \\ H_2SO_4$$

2. Anisole is more than 1000 times faster than benzene. Draw the mechanism, including all of the resonance structures for the cation intermediate in the p-bromination of anisole, and circle the "best" resonance structure.



2-Step Route to Add NH₂: 1) HNO₃, H₂SO₄ 2) Fe, HCl

- at nitro stage, Nitrogen is a meta director
- at amino stage, Nitrogen is an ortho-para director
- 3. Provide the reagents for the following transformation.



4. Design synthetic routes for the following transformations.



NH₂

Rules for Additions to Disubstituted/Polysubstituted Aromatics (17.9)

- 1. Effects are additive if both direct to the same spot
- 2. If there is a conflict of interest, the more activating group controls the outcome
 - You need to know the relative activating/deactivating strengths!
- 3. Steric considerations: if two substituents have a 1,3 (meta) relationship, addition in between
 - (to give a 1,2,3 relationship) is prohibitively slow for steric reasons

For each of the following, imagine what would happen if a mono-nitration took place. Would there be one main product, or more than one? If so, where?



3 H + R-X AlCl₃ (cat.) R (+ HCl) Activating Ortho/para a. Restricted to 3°, 2°, or ethyl halides. 1° halides suffer carbocation rearrangements. b. b. Since product is more active than starting material, polyalkylation is often a problem. c. Fails with strongly deactivated benzenes. Mech required.

FYI (not tested): Other Sources of Carbocations:

- $ROH + H_2SO_4$
- $ROH + BF_3$
- Alkene + H^+

Draw the Major Product and Mechanism for the Following (Assume a single substitution)



<u>Problem: Activating or Deactivating Effect by a Newly Added Substituent. Polysubstitution</u> <u>vs. Clean Monosubstitution. A thought exercise.</u>



What happens when the 2nd 50% of electrophile adds?

		Activating/Deactivating Effect	Amount	Amount	Amount
Case:	If: (hypothetically)	of Added Group "E"	of A	of B	of C
	Product " B " " is much	Activating			
1	more reactive than SM				
	" A "				
	Product "B" " is much	Deactivating			
2	less reactive than SM				
	" A "				
	Product " B " " is	No Effect			
3	equally reactive to SM				
	"A"				

Polyaddition Notes:

- 1. When a deactivator is added, monosubstitution is easy.
 - The adduct is always deactivated relative to the starting material
 - Most of the best aromatic substitutions add deactivators
- 2. When a donor is added, polysubstitution can be a factor.
 - Electronically, the adduct will be more reactive than the starting material.
- 3. Some solutions to polyaddition.
 - a. Perhaps di- or tri-addition is a good and desirable thing.
 - b. Use a huge excess of your aromatic starting material.
 - Benzene, toluene, or anisole for example, are cheap and can be used as solent.
 - The probability of an electrophile reacting with an adduct molecule may be statistically modest if there are thousands of times as many solvent starting materials available
 - c. Steric suppression. Often steric reasons can reduce the reactivity of the adduct.
 - Frequently the only available sites might be ortho to something or other, and experience at least some steric interactions
 - This may be increased with bulky electrophiles/substituents, as if often the case with 2° or 3° alkyl groups

<u>Practice Problem</u>: Assume each of the following are treated with (CH₃)₂CHBr (iPrBr) and AlCl₃. For each of the following:

- a. draw the product of the first substitution
- b. Draw the product of the second substitution (in other words, if the first product reacts again.)
- c. In every case, the second substitution will have some electronic advantage (because you just added an activator/donor.) But in which cases will the second substitution have a steric disadvantage?

H₃C a.

H₃CO OCH₃ b.

H₃CO₂C c.

2-Step Route to Add 1° Alkyl: 1) RCOCl, AlCl₃ 2) Zn(Hg), HCl

- at acyl stage, acyl carbon is a meta director
- at alkyl stage, alkyl is an ortho-para director
- 6. Fill in the blanks for the following reactions

Method 1: Direct F-C Alkylation



7. Design pathways for the following syntheses:





Sulfonylation/Reaction/Desulfonylation: 1. SO₃, H₂SO₄ 2. Whatever 3. H₂O, H₂SO₄

- Ideal procedure for when you have an ortho/para director, but you want an electrophile to end up ortho rather than para
- 8. Design pathways for the following syntheses:





9. Draw the products for the following reactions:



Oxidation of toluene methyl group (or other alkyl side chains): KMnO4

- The original alkyl group is an activating ortho-para director
- The resulting carboxylic acid is a deactivating meta director

10. Draw the outcomes for the following reaction sequences.



Benzylic Bromination Provides a Useful Functional Group:

- Treatment with many anions results in S_N2 substitution
- Treatment with bulky bases results in E2 elimination \rightarrow vinyl benzenes
- 11. Design pathways.



Synthetic Planning: To make multisubstituted aromatics, choose sequence with care!

<u>If:</u>	Make From:	
Para Disubbed	An ortho-para director (a donor)	
Meta Disubbed	A meta director (a strong, deactivating withdrawer)	
Ortho Disubbed	An ortho-para director and para position blocked using the	
	sulfonation/desulfonation trick	

Design Syntheses for the Following:



Design Syntheses for the Following:

